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THE MONTH

The Symposium

It is difficult to realize that it is just over fifty years ago that Starling first proposed the name 'hormone' for the secretions of the endocrine glands. Then, for all practical purposes, there were only two available to the clinician: adrenaline and thyroid extract. Today they seem to be legion and impinge upon every branch of the practice of medicine. That fashions change is as true of medicine as of millinery, and the chart of hormonal popularity is probably the most intermittent of all. Indeed, judging from the editorial and advertising pages of medical journals during the last decade, the traditional visitor from Mars would be justified in assuming that the only hormones still in use were of the cortisone family.

Not only have individual hormones waxed and waned in popularity. Like the vitamins, the whole group has tended to be surrounded with an aura of omnipotence and recommended for conditions in which there was no rational justification for their use. Perhaps the most notorious example of what can only be described as the abuse of hormones is the use of androgens to arrest the ageing process (particularly the loss of sexual potency), of œstrogens as a cosmetic agent, and of thyroid extract in the treatment of obesity. Unfortunately, the information about hormones tends to be dispersed in the scattered publications of the various specialties, which makes it difficult for the ordinary clinician to obtain a balanced and comprehensive review of their status. It is for this reason that we have devoted our first symposium of the New Year to this object. With the exception of adrenaline, all the hormones now in general use are included, with the emphasis upon the indications for their use.

The New Year

It is with heavy hearts that the profession enters upon the year that marks the end of the first decade of the National Health Service. Except in the imagination of what Sir Francis Walshe has described as those 'ephemeral Parliamentary figures that have held the office of Minister of Health' nothing has been gained, but much has been lost. The extent of the loss has too often been overlooked in the internecine wrangles over pecuniary adjustments which, to quote Sir Francis Walshe again, 'give colour to the gibe that we are interested in nothing other than remuneration'. Lack of statesmanship on the part of the profession has been as responsible as anything for the sorry pass to which the profession has now come. Too long has the profession lacked this lead now given by Sir Francis Walshe in the address on 'The Price of Freedom' which he delivered recently at the annual general meeting of the Fellowship for Freedom in Medicine (*Brit. med. J.*, 1957, **ii,** 1361).

Describing himself as one 'who is neither follower nor followed', Sir Francis presents a devastating analysis of the course of events during the past ten years. In essence, what has happened is that 'the permanent official is now in command, and for the first time in the history of his service he has got his claws well into a learned profession and he will not willingly let go'. Of more import to the profession are his criticisms of the Royal College of Physicians and of the British Medical Association; of the former for their President's 'unqualified' promise of 'firm and consistent cooperation with the government of the day'; of the latter for failing to have ready a report embodying a comprehensive survey and a series of practical suggestions for reform. There will be many who will agree with his contention that 'our purely academic corporations' should confine their intervention to professional and scientific questions. Too often in the past ten years have the profession's representatives allowed themselves to be so out-manœuvred by the politicians and civil servants that the only issue at stake appeared to be that of remuneration. What is now required—unless it is already too late—is a reorientation of policy with the emphasis upon principles and the safeguarding of those traditions which have for so long been the glory of British medicine but which are now threatened with near-annihilation.

Old Folks at Home

One of the interesting and welcome features of the intensive sociological investigations of the last decade has been the emphasis upon the importance of the family as the mainstay of the community. This is admirably brought out in a recently published survey by Mr. Peter Townsend of the old people of Bethnal Green ('The Family Life of Old People'. London: Routledge & Kegan Paul. Price 30*s*.). This is a fascinating study which exemplifies how such an investigation should be carried out and which provides a vivid picture of life in the East End of London at the present day.

Mr. Townsend's conclusions can be briefly summarized by two quotations from his book. 'So far at least as the old are concerned, there is no justification for an attempt to supplant the family with State services. Their job is to support the family and provide substitute help when it no longer exists'. 'We came to the conclusion that a comprehensive family help service, built on to the existing home help service and closely connected with the work of family doctors, may be the best . . . means of dealing with the lack of coordination and inadequacy of existing welfare services'. If the conditions obtaining in Bethnal Green are typical of other parts of the country, and there are no grounds for believing that they are not, the family tradition is still sufficiently strong to ensure that the family unit is capable, and willing, to look after its elderly members. All that they require in the way of help is assistance when the elderly become so infirm that constant nursing and supervision are required: for instance, sitters-in on one evening a week to allow the other members of the family to get out, or night sitters when 'grandmother' is difficult at night. The major problem is the infirm solitary

old person without any relatives or friends. Here some form of institutional supervision is probably necessary. This new approach to the care of the elderly is yet another challenge to the general practitioners of the country. It re-emphasizes that concept of him as the family doctor, to which the Ministry of Health pays lip service but does so little to encourage, although there have been recent signs that the Ministry is beginning to realize that what Mr. Townsend describes as 'a comprehensive family help service based upon the family doctor' is not only a cheaper, but also a more humane, way of helping the elderly than the present craze for institutions.

Whither WHO?

A TIME comes in the development of every new organization when it is essential that those in authority should take stock and decide whether its resources are being put to the best possible use. A recent report issued by the World Health Organization (WHO) suggests that in its zeal for planning it is beginning to lose its sense of proportion and to devote its energies to causes which have no reasonable justification. The report in question is of a body with the grandiloquent title of 'The WHO group on the mental health aspects of the peaceful uses of atomic energy'. Those 'participating' in this group were 'representatives of disciplines as different as psychiatry, atomic and radiation medicine, public health, social anthropology, and journalism'. It will be noted that neither general physicians, general practitioners, pædiatricians, nor school teachers were apparently represented.

This conclave of non-clinical experts solemnly decided that 'the complexity of underlying emotions in the changing environment of the second industrial revolution brought about by the atomic age needed to be recognized more widely among leaders of thought and action', and its first task is 'to establish what might be termed a culture of change in which change and reorientation would take place without upheaval'. What is not explained, and what would appear to be inexplicable to the ordinary clinician, is why the repercussion of atomic energy on mankind should be sufficiently different from the repercussion of any other major scientific advance to justify the setting up of a special committee of investigation. Surely it was not necessary for WHO to establish a special group to discover that 'the main duty of the present generation is towards its children', and that the upbringing of the latter 'must be free from anxiety and hate, producing in individuals self-reliance, and a sense of responsibility towards others'. Is this not what Christianity has been teaching for nigh on two thousand years, and what family doctors, clergymen, and teachers have accepted as the basis of the management of those entrusted to their care? To suggest, as WHO does, that the introduction of atomic energy has made any qualitative difference is the quintessence of obscurantism. The essential work of WHO is too important to allow it to be brought into ridicule by efforts such as this, and we trust that, for the sake of its good name, it will eschew any further unjustifiable ventures such as this.

Correspondence Courses for Patients

In 1947, the British Council for Rehabilitation established a Preparatory Training Bureau to provide correspondence courses for long-stay hospital patients. Over 2000 patients have enrolled for these courses, and during the last two years the scheme has been extended to include patients who are confined to their own homes because of long-term illness. An analysis of one year's working of the bureau by H. G. Maule (*Med. Offr*, 1957, **98**, 169) provides an interesting picture of the scope and extent of the work being done.

Of the 497 courses arranged in the year of the survey (1954), about a third (165) were commercial, whilst just under a third (138) were general educational subjects, with English and mathematics predominating. The remaining courses covered a wide range of subjects, ranging from mechanical engineering (39) to advertising and salesmanship (17). It is clear from this survey that even when the course was of no direct value from the point of view of the patient's subsequent career, it did, in the words of one patient, 'help by giving something concrete to work at through fourteen months of convalescence'. Dr. Maule is undoubtedly 'justified in saying with confidence that the Preparatory Training Bureau is playing a part both in aiding the long-term patient in his recovery, and in helping him to re-establish himself when he returns to normal working life'.

Minor Surgical Procedures

The series of articles on 'Equipping the Surgery' has aroused so much interest that we have decided to follow it with one on 'Minor Surgical Procedures'. This, logically, starts with a discussion of 'Local Anæsthesia' (p. 130) which will be followed throughout the year by a series of articles dealing with the common surgical conditions which are well within the province of the family doctor. Too often, since the introduction of the National Health Service, has the general practitioner solved the problem of there being a limit to what he could do in any one day by referring to hospital an increasing number of his patients with minor surgical conditions. Fortunately, the pendulum is now swinging in the opposite direction, and by reorganization, often by partnership and replanning of surgery accommodation, as described by Dr. Hughes in his James Mackenzie Lecture (p. 93), many practitioners are now finding that, not only can they cope with much of their own minor surgery, but also that it adds to the interest of their work. It is to meet the demand arising from this reorientation of general practice that we have planned this new series. It is only when the general practitioners of the country demonstrate in a practical way that they can cope with much of the minor illness that now causes congestion in outpatient and casualty departments, that the present undue emphasis on the hospital service will be rectified, to the consequent benefit of doctor, patient, and taxpayer.

THE ŒSTROGENS

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THIS article attempts to present a simple and practical survey of the therapeutic use of œstrogens. For this reason no account of original work is included and no references are given.

TERMINOLOGY

The term 'œstrogen' refers to any compound which produces effects on cells, tissues, organs or the behaviour of the individual as a whole which resemble those induced by the endogenous secretion of the hormone of the ovarian follicle, œstradiol. The term 'œstrin' is outdated and should be discarded. The term 'ovarian hormone' is ambiguous because there are two ovarian hormones and it might therefore apply to progesterone. Most pharmaceutical firms that distribute œstrogenic preparations attach a proprietary name to them. All these preparations consist of substances of known chemical structure and these proprietary names are therefore confusing in the majority of cases and should be avoided if possible. Exceptions can be made in cases in which the chemical name is complicated and difficult to remember, or where the preparation consists of a combination of œstrogenic substances such as the conjugated equine œstrogens extracted from pregnant mares' urine and marketed under the trade name 'premarin'.

PHYSIOLOGICAL ACTIONS

Œstrogens are responsible for the development of the female secondary sex characters and are essentially proliferative. They cause the Fallopian tubes to contract rhythmically and their fimbriæ to embrace the ovary at the time of ovulation so that the extruded ovum enters the tubal lumen. Œstrogens are responsible for the growth of the uterine muscle and its inherent tone, for the proliferation of the endometrium and for the secretion of a clear and copious fluid from the cervical glands. They bring about cornification of the vaginal mucosa, and the adult dimensions of the labia minora and majora. They are partly responsible for the growth of axillary hair and the female distribution of pubic hair. Under their influence the characteristic feminine contours of the body take shape and the ductal system and the connective-tissue elements of the mammary glands develop. They are responsible for the clear complexion and smooth skin of the female in contrast to the relatively greasy skin of the male. They stimulate osteoblastic activity and thus encourage the deposition of calcium and phosphorus in bone. They are also potent suppressants of pituitary activity and prevent the release of gonadotrophic hormones. This may lead to secondary failure of ovarian function, and especially inhibition of ovulation.

ŒSTROGENS AVAILABLE FOR CLINICAL USE

Œstrogens are either 'natural' or 'synthetic'. Natural œstrogens are extracted either from human sources or from the urine of pregnant mares. This is a costly process and natural œstrogens are expensive. Synthetic œstrogens are compounds produced in the laboratory and some of them, such as stilbœstrol, are very cheap. Others, such as dienœstrol, are moderately expensive, and yet others are almost as expensive as the natural œstrogens. The cheaper synthetic œstrogens are apt to produce toxic effects such as nausea and vomiting.

The following œstrogens can be obtained in this country at the present time:—

Natural œstrogens (Expensive)
- Œstrone. Œstradiol. Œstriol. Oral.
- Œstradiol monobenzoate. Intramuscular injection.
- Œstradiol dipropionate. Intramuscular injection.
- Œstradiol cyclopentylpropionate. Intramuscular injection.
- Œstradiol valerianate. Intramuscular injection.
- Conjugated equine œstrogens: 'premarin'. Oral.

Synthetic or partially synthetic œstrogens (Oral)
- Stilbœstrol (Cheap)
- Dienœstrol (Relatively expensive)
- Ethinylœstradiol (Cheap)
- Chlorotrianisene—'TACE' (Expensive)
- Methallenœstril—'vallestril' (Moderately expensive)

RELATIVE POTENCY OF THERAPEUTICALLY AVAILABLE ŒSTROGENS

The relative potency of several oral œstrogens has been established in the human being. It is therefore possible to give comparative figures of dosage for the following œstrogens:—

Stilbœstrol	1 mg.
Dienœstrol	5 mg.
Ethinylœstradiol	0.05 mg.
Conjugated equine œstrogen ('premarin')	2.5 mg.

The relative potency of chlorotrianisene and methallenœstril has not yet been determined. It is difficult to compare the potency of œstrogens administered parenterally with that of orally active œstrogens but it seems probable that œstradiol monobenzoate, given twice weekly (and œstradiol dipropionate at slightly longer intervals) in doses of 5 mg., corresponds with 1 to 2 mg. of stilbœstrol given daily by mouth.

ROUTES OF ADMINISTRATION

Oral œstrogens are effective in all circumstances and the indications for employing any other route of administration are therefore limited. Preparations designed so that the œstrogen shall be absorbed through the buccal mucosa directly into the systemic circulation are probably unnecessary. Intramuscular injection is confined to esters of œstradiol. The effect of œstradiol itself is transient, but its esters prolong its action. Œstradiol monobenzoate is effective for at least three days; the dipropionate for rather longer, and recently introduced esters, such as the cyclopentylpropionate

and the valerianate are said to promote œstrogenic activity for up to three weeks. Similar esters of œstradiol are prepared in the form of 'microcrystals' which are suspended in aqueous solution. Following intramuscular injection, absorption of the active material takes place slowly and constantly over a period of two or three weeks. Conjugated equine œstrogen is extracted from the urine of pregnant mares and is therefore water-soluble so that it can be given not only by mouth but also intravenously (in 20-mg. doses). The indications for the use of an ointment containing œstrogen are very limited; furthermore, it is difficult to concentrate the hormone in the ointment and the highest strength available is a 2.5 per cent. dienœstrol ointment. Suppositories may be used for local action on the vaginal mucosa. Finally, pellets of stilbœstrol or œstradiol for subcutaneous or deep intramuscular implantation are made up in doses of 50 or 100 mg. The duration of effectiveness of a stilbœstrol implant is from three to five months, whereas the effect of an œstradiol pellet lasts for 9 months to over a year.

TOXIC EFFECTS AND COMPLICATIONS

Toxic effects consist chiefly of nausea and vomiting although headaches, malaise and depression are sometimes experienced. These toxic effectsmost frequently occur with stilbœstrol, but they are also fairly often produced by ethinylœstradiol. Administration of dienœstrol, methallenœstril and chlorotrianisene is seldom accompanied by toxic effects, nor do the natural œstrogens such as œstrone and 'premarin' give rise to such symptoms. If the patient persists with the treatment toxic effects often wear off. The higher the dose the more likely is it to produce toxic effects, and doses of stilbœstrol of less than 1 mg. daily seldom produce nausea. On the other hand, such high doses of stilbœstrol or ethinylœstradiol as are given to arrest uterine bleeding or in the treatment of inoperable carcinoma of the breast are very likely to cause severe sickness. Toxic effects are never experienced during pregnancy and the puerperium and men complain of them less often than women.

The principal *complications* of œstrogen therapy are vaginal discharge, uterine bleeding, swelling and tenderness of the breasts, pigmentation of the nipples, and fluid and salt retention associated sometimes with a bloated feeling and gain in weight but seldom with actual œdema. The vaginal discharge is æsthetically unpleasant but in those patients in whom it tends to occur it cannot be avoided. Uterine hæmorrhage may take place while œstrogen is being administered ('break-through bleeding') or a few days after the end of a course ('withdrawal bleeding'). It is usually due to prolonged daily administration of œstrogen in moderate dosage; very high dosage suppresses pituitary activity so effectively that the consequent ovarian deficiency renders the endometrium atrophic and bleeding does not occur. The breast symptoms and fluid retention are also more likely to occur with prolonged treatment and high dosage, although some women are especially liable to develop tender, swollen breasts.

May exogenously administered œstrogen be carcinogenic? It is probable that endogenous œstrogen may play a part in the genesis of cancer of the breast and body of the uterus but there is little evidence that exogenously applied œstrogen is carcinogenic. There are a few sporadic reports of the development, in isolated cases, of cancer of the breast or uterus following œstrogen therapy, but our own experience in following up over 400 patients who have been treated with œstrogen over a period of more than six months is that only two developed cancer: one of the breast and the other of the uterus. A study of the experiments conducted on animals suggests that œstrogen would need to be administered continuously (rather than in intermittent courses as is the usual practice) over a period of some years before it is likely to be carcinogenic.

A consideration of the toxic effects and complications of œstrogen therapy, however, suggests that they are most likely to be avoided if dosage is kept as low as possible and if intervals of a week to ten days are allowed to elapse between successive courses which, with few exceptions, should last from two to six weeks. Should post-menopausal uterine bleeding occur while the patient is receiving œstrogen treatment the œstrogen is obviously the most likely cause; nevertheless, if there is the slightest doubt a diagnostic curettage should be carried out.

CLINICAL MANIFESTATIONS OF ŒSTROGEN DEFICIENCY

The most complete example of œstrogen deficiency is *gonadal agenesis* ('ovarian agenesis', 'Turner's syndrome'). In patients suffering from this condition, many of whom are genetic males, the gonad has been annihilated in early embryonic life before it has undergone differentiation. Such individuals develop along feminine lines but the absence of gonads results in such manifestations of œstrogen deficiency as primary amenorrhœa, an infantile uterus and small cervix, an atrophic vagina, absent labia minora, infantile labia majora, scanty pubic and axillary hair and complete absence of mammary development. Administration of œstrogen (either by implantation of two or three pellets of 100 mg. of stilbœstrol, with monthly courses of four daily injections of 25 mg. of progesterone, to produce withdrawal bleedings and prevent metropathic hæmorrhage, or by giving three-weekly courses of 3 mg. of stilbœstrol daily with intervals of a week between successive courses) leads to reasonably satisfactory breast development, which does not tend to regress once it is established, as well as cornification of the vaginal mucosa, maturation of the labia, increased growth of pubic and axillary hair and œstrogen withdrawal bleedings if the stilbœstrol is given in intermittent courses.

Although œstrogen will induce mammary development in these cases it is quite ineffective in increasing the size of *small breasts* in normal women.

THE CLIMACTERIC AND POST-MENOPAUSAL CONDITIONS

Whether the vasomotor or other symptoms of the climacteric are due to

over-production of pituitary gonadotrophins or simply to the gradual waning of ovarian function they can undoubtedly be controlled by œstrogen therapy. The lowest dose which will just control the flushes should be determined by trial and error and then maintained. It is always less than 1 mg. of stilbœstrol or its equivalent, and usually in the region of 0.25 mg. daily. Treatment should be discontinued every six weeks for a week or ten days. After some time it may be possible to allow the patient to take the maintenance dose for a few days from time to time when the flushes become tiresome and in this way she can be weaned from the treatment. In no circumstances should she be encouraged to take as many tablets as she thinks she needs. It is suggested that chlorotrianisene is especially effective in the treatment of the menopausal syndrome, for it is absorbed into the fat depots from which it is released in gradually diminishing concentration into the blood stream. It therefore simulates the waning function of the ovaries at the climacteric and it is claimed that two or three monthly courses may permanently cure the menopausal symptoms. It is further claimed that this tapering-off effect lessens the tendency to withdrawal bleeding, but this has not been our experience up to date.

Combinations of œstrogen and androgen are at present fashionable. Whatever the arguments may be in favour of this combined treatment one should be alive to the possibility of the development of hirsutism. The preparations on the market contain ethinylœstradiol, 0.01 mg., and methyltestosterone, 3 mg., per tablet and it is not considered unusual to take six tablets, giving a total of 18 mg. of methyltestosterone, a day.

The condition of *senile kraurosis* and *atrophic vaginitis* occurring often some years after the menopause responds well to œstrogen, preferably applied topically in the form of suppositories, or vulval inunction. *Senile osteoporosis* in women may be due to deficient activity of the osteoblasts; it is also to some extent caused by inadequate matrix formation. Combined treatment with œstrogen and androgen in the above dosage may help to arrest the osteoporosis and may indeed gradually lead to regeneration of the bone and lay down protein in the bony matrix upon which calcium phosphate can be deposited.

MENSTRUAL DISORDERS

It is fashionable to give œstrogen in doses of about 2 mg. of stilbœstrol daily, or its equivalent, for ten to fourteen days, or combinations of œstrogen and progesterone for three to five days, to induce withdrawal bleeding in cases of *amenorrhœa*. This seldom leads to the establishment of regular ovulatory cycles and is therefore of little value. It has been suggested that relatively large doses of œstrogen (such as 5 mg. of stilbœstrol daily) for about ten days may first suppress and then release gonadotrophin, thereby bringing about ovulation. Œstrogen in small doses, such as 0.5 mg. of stilbœstrol daily for twenty-one days together with 25 mg. of ethisterone for the last week of the course, has been suggested as an alternative to œstrogen therapy

alone, but often proves to be equally disappointing. Similar regimes are sometimes employed in cases of *oligomenorrhœa*, but it should first be established from a study of the basal temperature chart whether ovulation is taking place, as it often is in oligomenorrhœa, and if so endocrine therapy is probably redundant and may in fact suppress ovulation.

In *dysmenorrhœa*, ovulation can be suppressed by giving stilbœstrol, 2 mg. daily, or its equivalent, for fourteen days, starting within the first five days of the cycle. In the absence of a corpus luteum and secretion of progesterone the next period will be painless. Provided at least a week's interval elapses between successive courses there will be no untoward side-effects and the treatment may be repeated indefinitely.

The heavy and prolonged bleeding of *metropathia hæmorrhagica* can be arrested in about 70 per cent. of cases by giving an intensive course of large doses of œstrogen, such as 5 mg. of stilbœstrol or 0.2 mg. of ethinylœstradiol every two waking hours until the bleeding is appreciably controlled, usually within thirty-six hours. This is likely to give rise to severe sickness, and a more pleasant and usually more efficacious alternative is to give 20 mg. of 'premarin' intravenously. It may be necessary to repeat this two or three times at four- to twelve-hour intervals, depending upon the degree of hæmostatic response and the convenience of the patient and doctor. Unless this intensive treatment is tapered off by giving 5 mg. of stilbœstrol (or 0.2 mg. of ethinylœstradiol or 2.5 mg. of 'premarin') daily for a week, followed by 2.5 mg. of stilbœstrol (or 0.1 mg. of ethinylœstradiol, or 1.25 mg. of 'premarin') for a second week, there is considerable risk of a brisk withdrawal bleeding which may necessitate further hæmostatic treatment.

Moderate doses of œstrogen, such as 3 mg. of stilbœstrol daily for three weeks out of every four, have been advocated in cases of *functional uterine bleeding* in the hope of producing atrophy of the endometrium secondary to pituitary suppression.

Œstrogen has been used in *endometriosis*, principally to relieve the pain which is thought to be dysmenorrhœic in nature, the therapeutic regime being similar to that employed for dysmenorrhœa.

DISORDERS OF PREGNANCY

Œstrogen therapy in pregnancy has not lived up to the claims once made for it. It plays no part in the *induction of labour* or the relief of *uterine inertia*, although it may lead to evacuation of the uterus in cases of *missed abortion* and *missed labour*. A carefully controlled clinical trial showed that it is no more effective in lowering the fœtal mortality in cases of *pregnant diabetics* than is good nursing. The use of increasing doses of stilbœstrol, starting with 5 mg. daily at the 11th week and raising the dose by 5 mg. daily each week until 125 mg. are administered daily in the 35th week, for the prophylactic treatment of *toxæmia* and *eclampsia* is seldom used now in this country, nor is œstrogen much employed prophylactically in cases of *habitual abortion* or *threatened abortion*.

LACTATION

High levels of œstrogen inhibit lactogenesis (the initiation of lactation), probably by suppressing the production of prolactin: 15 mg. of stilbœstrol, or its equivalent, should be given on the day of parturition and the dose diminished to 10 mg. on the third day and to 5 mg. on the fifth day, treatment being suspended on the seventh day. If suckling is not maintained once lactation has become established, breast engorgement will develop. It may be possible to prevent this engorgement or to relieve it by giving œstrogen, but this is never so successful as is the inhibition of lactation by œstrogen.

CANCER OF THE BREAST AND PROSTATE

Breast.—The present teaching is to reserve œstrogen therapy in inoperable carcinoma of the breast for patients whose menopause has taken place at least five years previously. There is some disagreement concerning the optimal dosage. Most people would agree that it should not be less than 15 mg. of stilbœstrol or its equivalent daily, but much higher doses, such as 50 mg. or more daily, are sometimes employed. Œstrogen may favourably affect the primary growth or the soft tissue metastases but it also relieves the pain of bony metastases in some cases.

Prostate.—Here again there is no agreement as to optimal dosage, although probably 15 mg. of stilbœstrol daily is an adequate dose. Most people would reserve œstrogen therapy or orchidectomy until disabling symptoms appear, for there is evidence that in most cases the duration of effectiveness is limited and there is little evidence that œstrogen therapy instituted as soon as the diagnosis is made will affect the eventual course of the disease. On the other hand, œstrogen may produce sufficient shrinkage of a moderately large growth to enable it to be eradicated successfully by surgery.

IN THE MALE

The use of œstrogens in the male is limited, and effective treatment is usually accompanied by some degree of gynæcomastia, pigmentation of the nipples and testicular atrophy with diminished frequency of erections. Although both of these complications are completely reversible, the fact that they are likely to occur ensures that œstrogen therapy is not lightly undertaken. Œstrogen may be given prophylactically in cases of *mumps* occurring in adults so that if bilateral orchitis should develop the temporarily atrophied testes are not likely to be compressed by the tension which is normally exerted by the inexpansible tunica albuginea. Œstrogen has been employed in cases of severe *acne* and especially acne conglobata, where the scarring may be permanently disfiguring. The œstrogen suppresses the seborrhœa of the skin upon which the acne flourishes. Acne occurring in adolescent girls or young women may also be effectively treated by giving 3 mg. of stilbœstrol daily for three weeks out of every four. Œstrogen has been used in the management of *sexual offenders*, and indeed it can be guaranteed to render them impotent, in doses of 15 mg. of stilbœstrol or more daily. Some

claim, moreover, that œstrogen can significantly reduce the libido in hypersexual males.

Finally, œstrogen has been employed in the treatment of cases of *male transvestites*. The development of gynæcomastia and impotence does to some extent relieve the intolerable mental tension which they experience.

MISCELLANEOUS

Cervical mucus.—In some cases of infertility a negative post-coital test is obtained because the cervical mucus does not achieve that copious, clear physical consistency which is essential for the transport of the sperm into the uterus. This consistency can be induced by administration of small doses of œstrogen in the first half of the cycle: 0.25 mg. of stilbœstrol daily for fourteen days after the period starts.

Bucco-(vulval) ulceration.—The appearance of ulcers on the tongue, gums or buccal mucosa, very rarely accompanied by similar ulcers on the vulva, about a week before the period is due and their disappearance as soon as the period finishes, suggests that they may be manifestations of a lack of œstrogen. Œstrogen, given for three weeks out of every four, sometimes in quite high doses, often relieves the condition.

Progressive exophthalmos.—This is believed to be due to the excessive production of the exophthalmos-producing hormone (a variant of the thyroid-stimulating hormone) of the pituitary. Œstrogen is known to be a potent suppressant of pituitary hormone activity and has therefore been used in this condition—with rather equivocal results. Large doses, such as 5 mg. of stilbœstrol daily for six weeks at a time, are advisable.

SUMMARY

Œstrogens are 'proliferative' hormones which develop the secondary sexual characteristics of the female organism, stimulate osteoblastic activity and prevent the release of gonadotrophins.

A list of œstrogens available for therapeutic use in this country is given, together with their route of administration, relative potency and cost.

The toxic effects and complications which may result from œstrogen therapy are discussed and the best means of avoiding them is described.

The most extreme example of œstrogen deficiency is gonadal agenesis and the effects which may be produced by œstrogen therapy in patients suffering from this condition are described.

The management of the menopausal syndrome and post-menopausal manifestations by the use of œstrogens is outlined.

Œstrogens are usually ineffective in cases of amenorrhœa or oligomenorrhœa but they can prevent dysmenorrhœa by inhibiting ovulation and can arrest bleeding in metropathia hæmorrhagica. They play little part in the management of disorders of pregnancy, though they may be useful in the control of lactation.

Finally, they are employed in cases of inoperable carcinoma of the breast and prostate, and to a limited extent in certain disorders of males.

THE ANDROGENS

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An enormous literature has accumulated on the androgens in recent years. It has been most extensively reviewed by Dorfman and Shipley (1956) in a book of 590 pages devoted solely to this subject and the reader should consult this excellent monograph for further references. In this article it is proposed to review briefly two aspects only of the problem: the excretion of androgens and 17-ketosteroids in urine, and androgen therapy.

URINARY ANDROGENS AND 17-KETOSTEROIDS

Some confusion exists about the relationship between the androgens and the 17-ketosteroids. Androgens are substances which are capable of stimulating male secondary sexual characteristics; that is to say, they are defined by their biological activity and are measured by biological assay. The 17-ketosteroids, on the other hand, compounds characterized by having a steroid nucleus (fig. 1a) with a ketone at carbon 17 (fig. 1b), are defined by their chemical characteristics and are measured chemically.

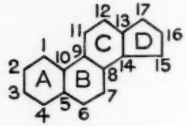
The amount of 17-ketosteroids excreted in the urine varies approximately with the amount of androgens. Since the chemical determination of urinary 17-ketosteroids is simpler than the biological assay of urinary androgens the former has been widely used as an indication of the latter. It must be realized, however, that not all androgens are 17-ketosteroids, as for example testosterone (fig. 1c), the chief naturally occurring androgen, which has been extracted from the testes. Nor are all 17-ketosteroids androgens. Some are inert whilst others have quite different biological activities, as for example the œstrogen, œstrone (fig. 1d). This substance, like the other natural œstrogens, has a phenolic ring A. Fortunately, these *phenolic* 17-ketosteroids are soluble in alkali and are easily removed from the main group of *neutral* 17-ketosteroids. They are not included therefore in the usual estimate of urinary 17-ketosteroids.

The metabolites which are measured in urine as *neutral* 17-ketosteroids bear only a superficial relationship to the androgens. They are mostly the by-products of metabolism of testicular and of andrenocortical steroids and are derived from these two sources in the proportions of roughly one to two. The absence of the testicular source accounts for the lower excretion of 17-ketosteroids by women, whose urinary output is roughly two-thirds that of men. Children excrete only very small quantities. The normal range for both sexes at all ages is read from the two graphs shown in fig. 2; they were published by Hamburger (1948) whose figures correspond closely with those obtained by other workers using similar methods.

THE CLINICAL SIGNIFICANCE OF URINARY 17-KETOSTEROIDS

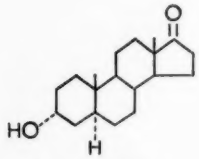
Urinary *neutral* 17-ketosteroids have been estimated in almost every known condition. The popularity of this estimate bears no relation to its clinical usefulness but is due to the belief that it is a good measure of adrenocortical function although rather a poor one of testicular function. The results of

numerous investigations are summarized briefly in table 1 which is extracted from the monograph of Dorfman and Shipley (1956). They are of necessity



Showing the standard lettering of the rings and numbering of the carbon atoms.

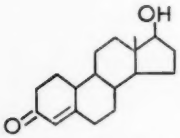
(a) The steroid nucleus



The ketone at carbon 17 is shown thus:—

A typical neutral 17-ketosteroid.

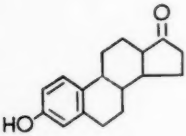
(b) Androsterone
(androstan-3-α-ol-17-one)



This is not a 17-ketosteroid because it has a hydroxyl at carbon 17 which is shown thus:—

but it has a ketone at carbon 3—it is a 3-ketosteroid.

(c) Testosterone



This is a 17-ketosteroid, but ring A is phenolic which is shown thus:—

(d) Œstrone

FIG. 1.—The chemical formulæ of the steroids and the androgens.

only very approximate but it will be seen that the most notable increase occurs in patients with adrenocortical carcinoma associated with virilism and next with adrenocortical carcinoma associated with Cushing's syndrome. Patients with adrenocortical hyperplasia associated with virilism or Cushing's syndrome show no increase or only a relatively small increase, except when the former occurs as a congenital disorder. There is a considerable overlap between these groups. Very high figures generally indicate malignancy but moderately high figures may leave the diagnosis of carcinoma in doubt. It has long been known that patients with malignant adrenocortical tumours excrete a β-17-ketosteroid, dehydroepiandrosterone, in relatively large amounts and it is possible to estimate the β-17-ketosteroids separately as a

group. Normally they constitute about one-tenth of the total 17-ketosteroids but in malignant forms of the disease they may constitute one-half. In patients with only a moderately increased output of 17-ketosteroids this estimation of the β fraction affords useful additional assistance in diagnosis.

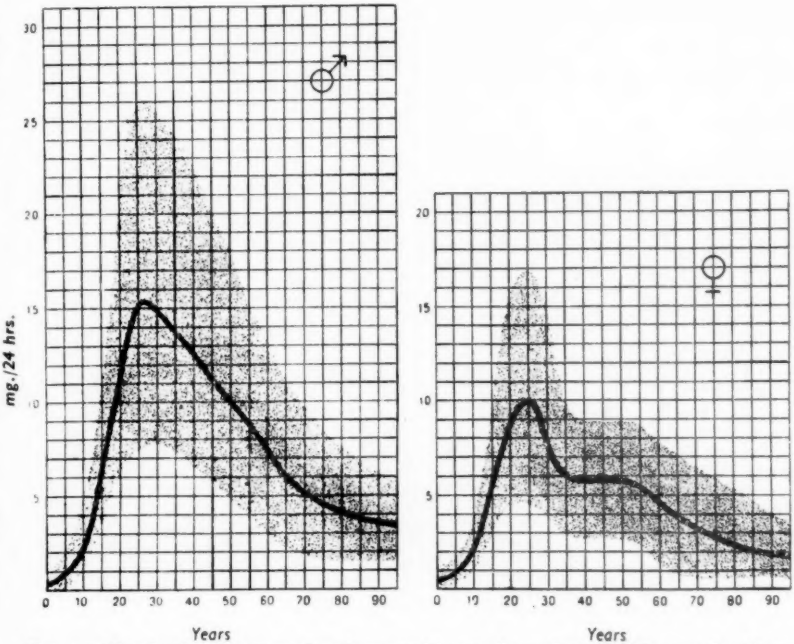


FIG. 2.—Graphs showing neutral 17-ketosteroid excretions of 264 healthy people. (Hamburger, 1948.)

The excretion of *neutral* 17-ketosteroids is notably increased in two other diseases, both of which are very rare: interstitial cell tumours of the testis, and a small proportion of ovarian tumours associated with virilism.

Perusal of table 1 will show that the excretion of 17-ketosteroids is altered in many other conditions, especially in Addison's disease and in Simmonds's disease. The estimation of urinary 17-hydroxycorticosteroids, however, gives a much more accurate and sensitive measure of adrenocortical function. This group of steroids constitutes biologically active corticoids and is much more selective than the conglomeration of substances which are measured as 17-ketosteroids. The estimation of 17-hydroxycorticosteroids should therefore supersede that of 17-ketosteroids for the study of adrenocortical function in these other disorders.

There is a notable exception to this statement. It concerns patients with congenital adrenocortical hyperplasia associated with pseudohermaphro-

ditism. This is a remarkable condition in which there is a failure to synthesize corticoids fully and, despite having huge adrenal glands, patients may die with adrenocortical insufficiency. Steroid synthesis is arrested prematurely at the stage of pregnanetriol, probably because of some enzyme deficiency,

Clinical condition	Comparison with normal adult level
Eunuchoid men	Half normal
Castrated men	Half normal
Ovarian agenesis	Half normal
Ovariectomy	No change or increase
Addison's disease:	
Men	One-third normal
Women	One-quarter normal
Panhypopituitarism:	
Men	One-sixth normal
Women	One-fifth normal
Acromegaly	No consistent deviation
Myxœdema	One-quarter normal
Thyrotoxicosis	Three-quarters normal to normal
Interstitial cell tumour of testis	5- to 100-fold increase
Masculinizing ovarian lesions	Usually normal, occasionally 4 to 10 times normal
Simple hirsutism	Above average normal
Adrenal hyperplasia—Cushing's	About twice average normal
Adrenal hyperplasia. Pseudohermaphroditism or male sex precocity	About 10 times normal
Cushing's—no definite adrenal tumour or hyperplasia	Less than twice average normal
Adrenal cancer—Cushing's	About 2 to 100 times normal, but may be normal
Adrenal tumour — Cushing's, not malignant	One-third to twice normal
Adrenal cancer—virilism	10 to 200 times normal
Adrenal tumour—virilism, not malignant	2- to 75-fold increase
Pregnancy:	
4th month	No change
8th month	About twice normal
Metastatic malignancy (not adrenal or gonadal)	About one-half normal
Malnutrition and anorexia nervosa	One-third to one-half normal
Diabetes mellitus (uncontrolled)	About one-half normal
Cirrhosis of liver	Variable reduction
Hypertension	About one-half normal
Rheumatic and collagen disease	Slight to moderate reduction
Homosexual men	No established difference from normal

TABLE I.—Excretion of 17-ketosteroids.

and a great excess of pregnanetriol and of various products of steroid catabolism including the 17-ketosteroids is excreted in the urine. Urinary pregnanetriol can be measured and gives a better estimate of the clinical state than 17-ketosteroids. It would be better therefore if this substance were measured, instead of 17-ketosteroids, in the urine of patients with congenital adrenocortical hyperplasia.

ANDROGEN THERAPY

A variety of androgens is now available for clinical use (table II).

The most widely used androgens are testosterone, testosterone pro-

pionate in oil for intramuscular injection, and methyltestosterone for oral administration. Testosterone and methyltestosterone implants were devised for prolonged action but they have been largely superseded by other long-acting preparations—testosterone isobutyrate, testosterone phenyl propionate and testosterone œnanthate for intramuscular injection—which seem to be very effective. An injection of 25 mg. of testosterone propionate three times a week, or 25 mg. of methyltestosterone by mouth daily or on alternate days, or an injection of 250 mg. of testosterone phenyl propionate every month or six weeks, is an adequate dosage for most purposes.

More recently, attempts have been made to find steroid substances which have weak androgenic activity compared with their protein anabolic activity. Some of these are now available on the market. They include methylandrostenediol, methylandrostenedioldipropionate, and methylandrostanolone, 19-nor-testosterone and 17-ethylhydroxy-19-norandrostenone. Their value in human disease, however, has not yet been adequately assessed.

Androgens have been used in a great many different clinical conditions, but with success in relatively few. They are most effective in clear-cut cases of androgen deficiency in the male, less so when they are used to antagonize other hormones, principally œstrogens, in women, and least when used for their protein anabolic action in certain diseases associated with protein deficiency.

PRIMARY MALE HYPOGONADISM
EUNUCHOIDISM AND CASTRATION

The response to treatment is often rapid. The patient first experiences erections and an increase in sexual desire. Soon the skin darkens, especially that of the penis and scrotum, and a slight reddening of the face may develop. Later the prostate enlarges and there may be an ejaculate. After a few months, axillary and pubic hair appears, but the latter usually fails to grow up towards the umbilicus and remains feminine in distribution. Hair appears on the face but rarely grows very strong and patients usually do not require to shave more often than every other day. A considerable increase in the dosage seems to have little more effect. The patients, however, feel stronger, often gain weight and are psychologically better balanced.

Secondary hypogonadism associated with pituitary insufficiency may develop in the absence of other evidence of pituitary failure but is difficult or impossible to recognize without assays of urinary gonadotrophins. The values are very low but in primary testicular failure they are abnormally high. Secondary hypogonadism is usually associated with other evidence of pituitary failure and is only a part of a more serious illness such as pituitary dwarfism or Simmonds's disease. These patients may respond to treatment with chorionic gonadotrophin but it is usually better to give them androgens and the improvement may be as marked as in primary hypogonadism. Pituitary dwarfs treated with androgens usually show a spurt in growth which may be pronounced. It is comparable with the spurt in growth which

Pharmaceutical name	Proprietary name	Manufacturer	Availability
Implants of testosterone B.P.	—	B.D.H.	100 mg.
	—	Organon	25 mg., 50 mg., 100 mg.
	Perandren	Ciba	100 mg.
	Virormone	Paines & Byrne	100 mg., 250 mg.
Testosterone sublingual tablets	Sublings	Organon	10 mg.
Testosterone aqueous suspension	Aquaviron	British Schering	25-mg. ampoules
	Micryston	Lab. for Applied Biology	15-mg. ampoules
Testosterone suppositories	—	Organon	15 mg.
Testosterone ointment	Perandren	Ciba	0.2%
	Perandren cream	Ciba	1%
	Testoviron cream	British Schering	0.2%
Testosterone propionate implants	—	B.D.H.	100 mg.
	—	Organon	100 mg.
	Sterandryl	Roussel	100 mg.
Testosterone propionate in oil	—	B.D.H.	5-mg., 10-mg., 25-mg., 50-mg., and 100-mg. ampoules
	—	Halewood	10-mg., 25-mg., 50-mg.. and 100-mg. ampoules
	Neo-hombreol	Organon	5-mg., 10-mg., 25-mg,, and 50-mg. ampoules
	Oxoid	Oxo	5-mg., 10-mg., 25-mg., 50-mg., and 100-mg. ampoules
	Perandren	Ciba	5-mg., 10-mg., 25-mg., 50-mg., and 100-mg. ampoules
	Sterandryl	Roussel	10-mg., 25-mg., 50-mg., and 100-mg. ampoules
	Testoviron	British Schering	10-mg., 25-mg., 50-mg., and 100-mg. ampoules
	Virormone	Paines & Byrne	5-mg., 10-mg., 25-mg., 50-mg., and 100-mg. ampoules
Testosterone propionate aqueous suspension	Testaform	B.D.H.	5-mg., 10-mg., 25-mg., and 50-mg. ampoules
	Virormone solcrysts	Paines & Byrne	50-mg. ampoules
Testosterone propionate ointment	Neo-hombreol	Organon	0.2%; 2.5%
Testosterone isobutyrate	Perandren M crystules	Ciba	50-mg. ampoules
Testosterone phenyl propionate	Tes. P.P.	Organon	10-mg. and 50-mg. ampoules
Testosterone oenanthate	Primoteston depot	British Schering	250-mg. ampoules

Pharmaceutical name	Proprietary name	Manufacturer	Availability
Testosterone œnanthate with propionate	Primoteston depot	British Schering	50-mg. and 100-mg. ampoules
Testosterone esters	Sustanon	Organon	100-mg. and 250-mg. ampoules
Tablets of methyltestosterone B.P.	—	B.D.H.	5 mg., 10 mg., 25 mg., 50 mg.
	—	Halewood	
	Oraviron	British Schering	
	Perandren	Ciba	
	Virormone	Paines & Byrne	
Sublingual tablets of methyltestosterone	Glosso-sterandryl	Roussel	5 mg., 10 mg., 25 mg., 50 mg.
	Perandren linguets	Ciba	
	Sublings	Organon	
Methylandrostenediol	—	Halewood	10 mg., 50 mg.
	Protandren linguets	Ciba	25 mg.
	Stenediol	Organon	10 mg., 50 mg.
Methylandrostenediol dipropionate	Methandiol glossettes	Roussel	10 mg., 25 mg.
Methylandrostanolone	Androstalone glossettes	Roussel	25 mg.
Epidehydroandrosterone	Diandrone	Organon	10 mg.
19-nor-testosterone phenyl propionate	Durabolin	Organon	25-mg. ampoules
17-ethylhydroxy-19-nor-androstenone	Nilivar	Searle	10-mg. tablets; 25-mg. ampoules

TABLE II.—Androgens for clinical use.

normally occurs at puberty and which is followed by closure of the epiphyses when further growth becomes impossible. Androgens hasten epiphysial closure in pituitary dwarfs and it is arguable whether the growth achieved is more or less than would ultimately have occurred if no treatment had been given, and this form of therapy is less popular than formerly.

Impaired sex drive and impotence are sometimes thought to be due to androgen deficiency but in the great majority of cases no deficiency can be demonstrated and treatment with androgens is very disappointing. Sterility with oligospermia or azospermia, which is unassociated with other evidence of organic disease, is rarely caused by androgen deficiency and there is no satisfactory evidence that it is cured by treatment with androgens. Androgens depress spermatogenesis in normal men. They have been used in the treatment of gynæcomastia but results have been disappointing. They have also been used for senility, arteriosclerosis and psychoses of men in middle and late life—with no proven success. They exacerbate male homosexuality.

ANDROGENS AS ŒSTROGEN ANTAGONISTS

Excessive uterine bleeding which is not caused by organic disease may respond to treatment with androgens. It is only when menorrhagia is associated with a proliferative type of endometrium or frank metropathia hæmorrhagica that success may be expected and the response is much greater when it is combined with large doses of progestogens. These should be given only for a short period in massive doses and never more often than once a month. Methyltestosterone, 25 mg., with ethisterone, 60 mg., three times a day for three or four days, rarely fails to control it. It has the effect of cleaning out the endometrium like surgical curettage but the patient must be warned that bleeding will continue for a few days until this process is complete. Afterwards there is a normal interval before the next period begins. In bad cases it is often necessary to repeat the treatment, starting on the first day of each period for several months in succession. Continuing treatment for longer than four days at a time prolongs bleeding and defeats its own end. The only risk is the development of facial hirsutism but this has never been observed when treatment at this dose level has been confined to four days each month. Excessive bleeding associated with a secretory type of endometrium does not respond to such combined therapy.

Endometriosis.—Aberrant endometrial tissue shrinks under the influence of androgens and the pain is often relieved when 25 mg. of methyltestosterone is given daily by mouth for the two weeks preceding menstruation. Unfortunately this dosage may lead to the growth of facial hair.

Premenstrual tension.—A variety of symptoms occurs in this disorder but nervous or psychotic ones are the most serious. These sometimes respond well to methyltestosterone by mouth in a dosage of 10 to 25 mg. daily for five to ten days before each menstrual period.

Dysmenorrhœa.—Given in sufficient dosage androgens cause anovular menstruation which is painless, but the dosage usually has to be large and masculinization ensues.

Frigidity and homosexuality.—Androgens increase libido to a much greater extent than do the female sex hormones and have been used successfully in the treatment of frigidity in the female. They have the same effect in homosexual women but do not alter the direction of the sex drive and therefore lead to an exacerbation of symptoms.

Post-partum breast engorgement.—It is claimed that androgens relieve the pain in the great majority of cases of breast engorgement and that the flow of milk is not suppressed so long as suckling continues.

Mastalgia.—Pain in the breast associated with chronic mastitis is often relieved by androgens. The dosage required may be large and masculinization ensues.

Carcinoma of the breast.—Androgens have now been used for the treatment of cancer of the breast long enough to assess their value fairly accurately. The dosage recommended varies between 25 and 100 mg. of testosterone propionate by intramuscular injection three times a week, or

up to 100 mg. of methyltestosterone orally each day. Larger doses are no more effective despite the development of hirsutism. Treatment must be continuous because cessation may lead to rapid deterioration. It causes a rapid relief of pain, an increase in appetite and a gain in weight in more than half of the patients but objective evidence of improvement occurs in only about one-fifth. There may be a diminution in the size of metastases in the soft tissues or radiological evidence of regression of the bony lesions. The improvement in the length of survival, however, is disappointing, the average survival being only about three months longer in those who respond than in those who fail to respond to treatment. The age of the patient makes little difference to the response. Several of the new protein anabolic hormones have been used for cancer of the breast in the hope that they might be as effective as testosterone without having its masculinizing action, but the evidence suggests that their effectiveness varies with their androgenic potency.

PROTEIN ANABOLIC HORMONES

Senile osteoporosis is believed to be due to deficiency of protein matrix in bone. The matrix is the scaffold upon which calcium salts are deposited and when it is deficient there is a proportional deficiency of calcium salts. The protein matrix is believed to be under the influence of protein anabolic hormones and treatment with testosterone causes a retention of calcium as well as of protein. The radiological change induced in osteoporotic bone by therapy with protein anabolic hormones, however, is very slow—due, perhaps, to the fact that it may take several years to restore the lost calcium.

Cushing's syndrome is associated with a gross loss of protein and attempts have been made to treat this condition with testosterone. The correct treatment, however, is surgical.

Addison's disease has also been treated with androgens but this seems to be unnecessary with adequate corticoid therapy.

Androgens have been used in many other conditions with doubtful results. These include trauma, nephrosis, liver disease and premature infants.

COMPLICATIONS

The most serious complication of androgen treatment is masculinization in the female. It is always wise to warn patients of this risk. Another and sometimes serious complication is retention of salt and water causing frank œdema. This may be dangerous in patients with congestive heart failure. It also causes a depression of spermatogenesis, but this effect subsides after cessation of treatment. It may exacerbate cancer of the prostate and of the male breast, and it is claimed that methyltestosterone may occasionally cause jaundice.

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CORTISONE AND HYDROCORTISONE

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Cortisone and hydrocortisone belong to the 11-oxysteroid group of adrenal corticosteroids, so-called because an oxygen atom occupies position 11 in the steroid ring. Hydrocortisone is secreted by the human adrenal cortex in greater amounts than any other adrenocortical hormone; cortisone, on the other hand, is not produced by the adrenal glands, but is probably formed from hydrocortisone in small amounts elsewhere. When cortisone is administered by mouth or by injection, it is probably converted into hydrocortisone, which is the active hormone. Both hormones are prepared synthetically.

The output of hydrocortisone is increased by the injection, or by excessive secretion, of the anterior pituitary hormone, corticotrophin (ACTH), and is decreased by removal of, or damage to, the anterior pituitary lobe or the adrenal cortex or by a defect of one of the adrenal enzyme systems concerned in its biosynthesis.

PRINCIPAL ACTIONS

The actions of cortisone and hydrocortisone are similar, hydrocortisone being about 20 per cent. more potent than cortisone. Physiologically, one of the principal actions of hydrocortisone is to play a part in regulating carbohydrate metabolism: for this reason it is termed a glucocorticoid. It raises the level of the blood sugar by decreasing the utilization of glucose and by converting amino-acids into glucose (gluconeogenesis). It also promotes filtration by the glomeruli and thereby maintains urinary flow. It is because of lack of this function that patients with adrenal insufficiency are unable to produce a water diuresis. An important function of hydrocortisone is to increase the ability of the body to withstand stress produced by whatever agent, for instance, trauma, an infection, exposure to cold, or undue exertion, and in these circumstances its output is greatly increased.

When present in excess, cortisone or hydrocortisone produces hyperglycæmia and glycosuria. On protein they have either a catabolic or an anti-anabolic action; some workers believe that they diminish the anabolism of protein by converting amino-acids into glucose, thus reducing the amino-acids available for the synthesis of protein. When patients are subjected to excess of the hormones for a prolonged period, reduction of protein anabolism leads to defective repair of the tissues; consequently, spontaneous bruising, purple striæ and osteoporosis may result. In the young they retard growth. In excessive amounts they alter the distribution of fat and produce

obesity of the type occurring in Cushing's syndrome. They may also cause retention of sodium and loss of potassium in the urine.

When given in large amounts the hormones suppress the normal inflammatory response, disturb the process of wound healing, diminish the permeability of capillaries and membranes and favour the spread of infection (not to be confused with the resistance they produce to the *stress* of infection). They are also anti-allergic.

AVAILABLE PREPARATIONS

Cortisone.—Cortisone is administered as the acetate and is available as:—

(a) Scored tablets (5 mg. and 25 mg.).

(b) Microcrystalline suspension in sterile isotonic saline (25 mg. per ml.) for intramuscular injection.

(c) Ointment (1 per cent.)
(d) Eye-drops (1 per cent.) } for ophthalmic use.

Hydrocortisone.—Hydrocortisone may be obtained as:—

(a) Hydrocortisone free alcohol tablets (10 mg. and 20 mg.).

(b) Hydrocortisone free alcohol in 50 per cent. ethyl alcohol (vials containing 100 mg. per 20 ml.) for intravenous injection; the preparation must be diluted with 1 or 2 pints (0.5 to 1 litre) of physiological saline or a 5 per cent. solution of dextrose in water or saline, depending upon the condition for which it is used.

(c) Hydrocortisone acetate as a crystalline suspension in isotonic saline (25 mg. per ml.) for injection into joints and bursæ.

(d) Hydrocortisone acetate ointment (0.5, 1, and 2.5 per cent.) for skin and eye diseases.

(e) Hydrocortisone acetate eye-drops (1 per cent.).

(f) Hydrocortisone lotion (0.5 and 1 per cent.) and hydrocortisone spray (0.5 per cent.) for skin diseases.

ADMINISTRATION

Cortisone acetate in suspension should never be injected intravenously. Cortisone applied to the eye or injected into a joint is less prompt and less effective in its action than hydrocortisone, probably because it has to be converted into the latter hormone: preparations of hydrocortisone are therefore employed. Cortisone, unlike hydrocortisone, is ineffective when applied locally to the skin for various skin diseases.

The intravenous infusion of hydrocortisone free alcohol, producing a rapid effect, is intended for use in an adrenal crisis or to meet acute stress in cases of adrenocortical insufficiency. As it is rapidly eliminated from the body its action does not continue for long after the infusion has been stopped and therefore it should be supplemented with intramuscular injections of cortisone acetate which, being slowly absorbed, have a more prolonged effect.

Cortisone acetate is more rapidly absorbed when given by mouth than

when injected intramuscularly and hence the oral route does not produce quite such a sustained concentration in the blood as the intramuscular. In spite of this slight disadvantage, for maintenance therapy oral administration is usually adopted because of its convenience. Hydrocortisone acetate is ineffective administered orally because of its low solubility, whilst free hydrocortisone given by mouth is more rapidly eliminated from the body than cortisone acetate, thus necessitating more frequent administration: e.g. four-hourly.

CLINICAL INDICATIONS

Treatment with cortisone and/or hydrocortisone is employed: (1) as replacement therapy in adrenocortical insufficiency, (2) to suppress excessive production of adrenal androgens in the adrenogenital syndrome and (3) in certain diseases without evidence of adrenal deficiency.

ADRENOCORTICAL INSUFFICIENCY

Adrenocortical insufficiency occurs in Addison's disease, in the Waterhouse-Friderichsen syndrome, after bilateral adrenalectomy for mammary carcinoma and Cushing's syndrome, after the removal of an adrenal tumour (usually for Cushing's syndrome), and secondary to hypopituitarism. It may also occur on sudden withdrawal of cortisone in patients treated with large doses for a prolonged period. In these conditions cortisone is merely a replacement therapy repairing a deficiency and has no side-effects if given in the proper dosage. The physiological requirement of cortisone in an adult person is about 25 mg. a day.

In chronic adrenocortical insufficiency without complications cortisone acetate is given by mouth, at first in doses of 50 mg. daily for an adult, in three divided doses eight-hourly, the early morning dose being 25 mg. and the two subsequent doses 12.5 mg. When a full response has been obtained the dose is gradually reduced to the maintenance dose of 12.5 mg. twice daily: heavier persons may need it three times daily. After the response to cortisone has been effected, the treatment is supplemented in cases of primary adrenal insufficiency with small doses (1 to 2 mg. daily) of deoxycortone acetate because of deficiency of the powerful salt-retaining hormone, aldosterone, and the inadequate salt-retaining potency of such low doses of cortisone. When the patient is balanced on deoxycortone the hormone may be implanted as pellets, 100 to 200 mg. every eight months, or it may be injected intramuscularly as the trimethylacetate every four weeks in doses of 25 to 75 mg. Deoxycortone may not be quite so necessary in adrenal deficiency secondary to hypopituitarism because the secretion of aldosterone is not entirely under the control of corticotrophin, but such patients often feel better as a result of its administration. Because of its blood-pressure-raising action it should not be employed in patients whose blood pressure is above normal.

Should a *secondary infection* arise the dose of cortisone should be increased up to 100 to 150 mg. daily.

Surgery.—If a patient with chronic adrenal insufficiency is to undergo a surgical operation, or if bilateral adrenalectomy or the removal of an adrenal tumour is to be performed, the following procedure is carried out. One hundred milligrams of cortisone acetate are injected intramuscularly twelve hours and again two hours before the operation and the administration of an antibiotic is started to ward off infection. During the operation 100 mg. of hydrocortisone free alcohol in a litre of 5 per cent. solution of dextrose in water are infused intravenously by drip which is continued for six hours. Cortisone acetate is injected intramuscularly in doses of 50 mg. six-hourly for twenty-four hours, then eight-hourly for forty-eight hours and then twelve-hourly for forty-eight hours. Thereafter cortisone acetate is given by mouth, 25 mg. eight-hourly for two or three days, after which the dose is gradually reduced to the maintenance dose.

Pregnancy.—If there is much vomiting in the early months of pregnancy in a patient with adrenal deficiency the dose of cortisone should be increased; intramuscular injections may be necessary in doses of 100 mg. daily. The same regime is adopted for labour as for a surgical operation.

Addisonian crisis; hypopituitary coma.—The treatment of these conditions is similar to that described in the case of a patient undergoing surgical procedures, except that, should hypoglycæmia be present, 50 ml. of 50 per cent. dextrose in water are injected at once intravenously and the hydrocortisone free alcohol is diluted with physiological saline.

ADRENOGENITAL SYNDROME

In the absence of an adrenocortical androgen-producing tumour the adrenogenital syndrome is associated with congenital or acquired adrenocortical hyperplasia. In infants the condition presents either as female pseudohermaphroditism or as virilism in females and as macrogenitosomia præcox in males. It is probably due to failure of the enzyme system in the adrenal cortex which normally converts 17α-hydroxyprogesterone into hydrocortisone. Deficiency of hydrocortisone leads to increased secretion of corticotrophin which produces the hyperplasia and an increased output of androgens. The administration of cortisone in adequate doses suppresses the secretion of corticotrophin and thereby reduces the production of androgens. The treatment retards genital growth in males and may produce mammary development and regular menstruation in older females; the effect on the hirsuties, however, is often disappointing.

Dosage.—For patients of 8 years of age and over, 50 mg. of cortisone acetate and for younger patients 25 mg. are injected daily. When the urinary 17-ketosteroids have fallen to normal, the dose is reduced to the minimal dose which will maintain this level. This may be 25 mg. intramuscularly daily for children over the age of 8 years and 5 mg. daily for infants. If cortisone is given by mouth two or three times these doses may be necessary (Wilkins, 1952). Fortnightly intramuscular injections of hydrocortisone acetate in doses of 250 mg. for older children and young adults maintain

effective suppression of corticotrophin (Spence *et al.*, 1956).

DISEASES WITHOUT EVIDENCE OF ADRENOCORTICAL INSUFFICIENCY

The principal diseases under this heading which may be benefited by cortisone or hydrocortisone therapy are as follows:—

Allergic conditions—angioneurotic œdema, drug sensitivities, hay fever, serum sickness, status asthmaticus.

Arthritic conditions—ankylosing spondylitis (early), Felty's syndrome, rheumatic fever, rheumatoid arthritis, osteoarthritis, Still's disease, traumatic arthritis.

Blood diseases—acquired hæmolytic anæmia, acute lymphatic leukæmia, agranulocytosis, idiopathic thrombocytopenic purpura.

Collagen diseases—acute dermatomyositis, disseminated lupus erythematosus, polyarteritis nodosa, scleroderma (early), temporal arteritis.

Eye diseases—acute inflammatory eye diseases, allergic conjunctivitis, sympathetic ophthalmia.

Gastro-intestinal diseases—idiopathic steatorrhœa, regional ileitis, ulcerative colitis.

Lung diseases—Lœffler's syndrome, pulmonary granulomatosis, sarcoidosis.

Metabolic diseases—acute gout, idiopathic hypercalcæmia of infants, idiopathic hypoglycæmia.

Nervous diseases—acute polyneuritis, retrobulbar neuritis, toxic encephalitis.

Renal conditions—the nephrotic syndrome.

Shock—acute peritonitis, burns, surgical shock.

Skin diseases—allergic dermatitis, ano-genital pruritus, atopic dermatitis, Besnier's prurigo, contact dermatitis, eczema, exfoliative dermatitis, pemphigus, urticaria.

Soft-tissue-lesions—acute bursitis, acute plantar fasciitis, Dupuytren's contracture, tennis elbow, tenosynovitis, trigger finger.

DISADVANTAGES AND LIMITATIONS OF CORTICOSTEROID THERAPY

Whilst corticosteroid therapy may be life-saving in certain cases and be of considerable benefit in others, it should be emphasized that it does not remove the basic cause of the disease: it merely abolishes the tissue reactions of the disease and the symptoms which result from these reactions. Thus, unless the disease has run its course, relapse will take place if the treatment is terminated. Except when local therapy is employed, as in diseases of the eyes and skin, the doses necessary to effect improvement are much above the physiological requirements and therefore with prolonged treatment there arises the supreme disadvantage of side-effects which may be as serious as the disease itself. In these circumstances the clinician must decide

whether the disease is severe enough to warrant corticosteroid therapy or whether there is some other method which is equally or almost as effective. If long-term corticosteroid therapy is decided upon, it is advantageous to give a dose sufficiently low to produce relief of symptoms to a degree of 50 to 75 per cent. in order to reduce the liability to side-effects. This does not arise in the treatment of a condition such as status asthmaticus in which the period of corticosteroid therapy is short and in which high doses may be given without ill-effect.

Side-effects of systemic therapy.—Side-effects do not arise with topical therapy. On the other hand, nearly all patients receiving a daily dose of 75 to 100 mg. of cortisone systemically will in time develop some side-effect or other. The side-effects which may arise are as follows:—

(1) Rounding of the face such as occurs in Cushing's syndrome. This is due to the accumulation of fat. Fat may also be deposited on the nape of the neck and on the abdomen.

(2) Sodium retention and œdema: this may be prevented or reduced by giving a low-sodium diet.

(3) Convulsions, especially in children, probably due to water retention.

(4) Loss of potassium resulting in muscular weakness. The blood level of potassium may be maintained by giving 3 to 5 g. of potassium chloride daily.

(5) Gain in weight, due to fluid retention and fat.

(6) Hyperglycæmia and glycosuria through the conversion of amino-acids into glucose and impaired utilization.

(7) Hypertension and congestive heart failure.

(8) Acne, amenorrhœa and hirsutism: these symptoms arise because a small amount of cortisone is converted into androgen.

(9) Sleeplessness.

(10) Psychological changes: the commonest is euphoria, but sometimes depression occurs. Disorientation, aggressiveness, hypomania and suicidal tendencies have been observed.

(11) Purple striæ on the abdomen and hips and spontaneous bruising, both conditions being due to lack of amino-acids for tissue repair.

(12) Osteoporosis, especially of the spine, and spontaneous fractures, due to lack of amino-acids and inhibition of osteoblastic activity.

(13) Alteration in tissue reactions:

- (a) Perforation or bleeding of peptic ulcers; perforation of the colon in diverticulitis.
- (b) Increased susceptibility to infections.
- (c) Masking of symptoms of infections.
- (d) Aggravation of tuberculosis through failure of local tissue defence reactions.
- (e) Delayed healing of wounds.

(14) Adrenocortical atrophy due to suppression of corticotrophin.

Many deaths directly attributable to corticosteroid therapy have been

reported, the commonest cause being infection and the next in order gastro-intestinal hæmorrhage and perforation (Allanby, 1957).

CONTRAINDICATIONS TO SYSTEMIC THERAPY

Cortisone and hydrocortisone should *never* be employed systemically for diseases complicated by peptic ulcer, diverticulitis, chronic nephritis, Cushing's syndrome, psychoses, tuberculosis, infectious diseases not controlled by antibiotics and virus diseases such as poliomyelitis, chickenpox and vaccinia.

Corticosteroid therapy may have a deleterious effect when the disorder for which it may be indicated is complicated by any of the following conditions: congestive heat failure, hypertension, ischæmic heart disease, infections, diabetes mellitus, osteoporosis, convulsive disorders (except spontaneous hypoglycæmia), thrombosis, pregnancy and a past history of mental disorder (Hench and Ward, 1954). In such cases judgment should be used as to whether such treatment is justified.

DOSAGE AND METHODS OF TREATMENT

In those conditions in which systemic therapy is indicated cortisone acetate is given by mouth at six- or eight-hourly intervals. During the first week or fortnight the doses should be high, in order to induce rapid remission. The dosage depends upon the severity of the disease, the duration of treatment, the presence of a relative contraindication and the age of the patient. Depending upon the condition that is being treated, the initial dosage varies from 100 to even 400 mg. daily and the duration of these initial high doses also varies. After a full response has been obtained the dose should be gradually reduced by 2.5 to 5 mg. daily to the minimal effective dose, which may be 50 to 75 mg. daily. As already mentioned, it may often be advisable to achieve only partial control of the disease in order to avoid side-effects.

Adjuvant therapy applicable to the particular disease should be employed. If cortisone therapy is to be prolonged the patient should receive a high-protein, low-sodium diet and 3 to 5 g. of potassium chloride a day. Before the treatment is started inquiry should be made into a previous history of dyspepsia, and the chest should be examined radiologically for tuberculosis. During treatment the blood pressure should be taken and the urine tested for glucose periodically.

Because unphysiological doses of cortisone cause adrenocortical atrophy, the dose of cortisone should be still further increased during and after a surgical operation, after trauma and during a secondary infection, as described for adrenocortical insufficiency. In actual practice the effect on the healing of wounds is negligible.

When it is decided to withdraw systemic cortisone therapy, the dose of cortisone should be gradually reduced over a period of two weeks, in order to prevent symptoms of adrenocortical insufficiency. On the two days before treatment is stopped corticotrophin gel or corticotrophin zinc should be

injected intramuscularly in doses of 40 units twice daily and should be continued in reducing dosage for the next three days. In spite of this precaution some degree of adrenal insufficiency may persist for many months. Should such patients be subjected to the stress of an infection or surgery during this period they should be given cortisone in doses of 100 to 200 mg. a day. After the period of stress cortisone should be withdrawn gradually over the next two weeks.

ASTHMA AND HAY FEVER

Patients in *status asthmaticus* who have not responded to other measures require large doses of cortisone. The dosage employed by a subcommittee of the Medical Research Council (1956b) was 50 mg. immediately, followed by 25 mg. hourly for eight hours and then four-hourly, the total dose on the first day being 350 mg. On the second day the dose was 50 mg. six-hourly and during the next seven days it was reduced by 25 mg. a day. Cortisone is not recommended in *chronic asthma* because of its suppressive effect on corticotrophin. It should be reserved for the acute and severe phases of the disease when antispasmodics have failed (M.R.C. Report, 1956a). Satisfactory results have been obtained in *hay fever*, unresponsive to other forms of therapy, with a snuff of hydrocortisone acetate (Herxheimer and McAllen, 1956).

RHEUMATIC DISEASES

Only selected cases of *rheumatoid arthritis* should be treated with cortisone, since the results with aspirin appear to be as good. The initial dose is 100 mg. of cortisone daily for a week; this is gradually reduced to 50 mg. daily. If only one or two joints are affected, or if one joint is outstandingly painful, 0.5 to 2 ml. of hydrocortisone acetate in saline suspension injected into the joint brings about improvement for one to four weeks. In *rheumatic fever* cortisone is rarely required, for there is so far no proof that it prevents or reduces cardiac damage. In severe cases it may have to be given in doses of 200 to 300 mg. daily for four weeks with gradual reduction in dosage (Polley, 1956).

Arthritic conditions (gouty arthritis, traumatic arthritis and osteoarthritis) are treated by intra-articular injections of hydrocortisone acetate in saline suspension at intervals of two to four weeks. The results are better in arthritis of the knee than of the hip because of the difficulty in injecting the latter; the treatment is ineffective in those joints without a synovial cavity (Hollander, 1953). Non-arthritic *soft-tissue lesions* are also much improved by local injection of hydrocortisone acetate (Cyriax, 1953; Crisp and Kendall, 1955).

BLOOD DYSCRASIAS

In *acquired hæmolytic anæmia* and in *idiopathic purpura hæmorrhagica* systemic treatment with cortisone produces favourable results in a high proportion of patients (Dameshek, 1952; M.R.C. Report, 1953). The initial

doses are 100 to 300 mg. daily; the dose is gradually reduced when a response has been obtained. In *acute and subacute lymphatic leukæmia* cortisone is given in doses of 200 to 300 mg. daily in adult patients and up to 200 mg. daily in children; although a satisfactory response may be obtained, relapse occurs after a few weeks.

POLYARTERITIS NODOSA AND ULCERATIVE COLITIS

Cortisone therapy usually produces rapid improvement in *polyarteritis nodosa*, but large doses are required, giving rise to troublesome side-effects. The initial dose is 200 mg. daily for one week and, if possible, this should be gradually reduced (M.R.C. Report, 1957).

In *ulcerative colitis* the introduction into the rectum of a solution of 250 mg. of hydrocortisone free alcohol in 50 ml. of 50 per cent. ethyl alcohol, diluted with 500 ml. of normal saline, by slow drip nightly for two to three weeks, may produce rapid, though temporary, improvement within a few days (Truelove, 1956).

SKIN DISEASES

Most of the skin diseases previously mentioned respond to topical therapy in the form of hydrocortisone ointment or lotion applied as a spray. In *pemphigus* large doses are necessary, e.g. 300 to 400 mg. daily, to produce effective control, but as the disease is usually fatal it is an absolute indication for prolonged cortisone therapy (McGehee and MacLean, 1954).

CONCLUSION

In conclusion, I would emphasize that cortisone in the high doses required for non-endocrine diseases is a dangerous drug and for this reason should only be employed by physicians experienced in its use.

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PREDNISONE AND PREDNISOLONE

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THE discovery of cortisone and hydrocortisone led to a period of trial and error in assessing their worth as therapeutic agents in a variety of disorders. The three main uses were:—

(1) As local agents—hydrocortisone applied to the skin or injected into a joint, cortisone or hydrocortisone applied to the outer eye.

(2) In endocrine disorders, such as Addison's and Simmonds's disease, as replacement therapy.

(3) As symptom-suppressing agents in a large variety of inflammatory disorders, ranging from rheumatoid arthritis and status asthmaticus to angioneurotic œdema.

It was particularly in the last group that undesirable effects became rapidly apparent; to call them 'side' effects is hardly correct, for the features of Cushing's syndrome are the natural result of overdosage. Used as hormones in replacement therapy in small but adequate dosage such effects are slight or absent; pushed above this level some features of Cushing's syndrome will occur in almost every case if treatment is continued for more than a few days. In addition, peptic ulceration and its complications, not common features of Cushing's syndrome occurring naturally, are seen more and more frequently as dosage is raised. Indeed, these gastro-duodenal complications are the main hazard in cortisone symptom-suppressing therapy. It was in an effort to find new steroid substances which had fewer such undesirable effects, while retaining the therapeutic effectiveness of cortisone and hydrocortisone, that many workers, particularly in the United States, tried to modify their molecular structure in a variety of ways.

HISTORY

Fried (1956) has stated that the so-called 'antirheumatic' or anti-inflammatory properties of cortisone and its analogues depend upon:—

(1) a 3-keto, 4, 5 unsaturated structure in ring A

(2) an oxygen atom at position 11, and

(3) a dihydroxyacetone side chain at position 17.

Whilst these three essentials were retained a variety of other changes was made and it was discovered that, whereas the introduction of a double bond between carbons 6 and 7 resulted in a loss of therapeutic (anti-inflammatory) potency, the introduction of such a double bond between carbons 1 and 2 produced a marked increase in therapeutic effect without causing any change in the compound's salt-retaining or potassium-losing (so-called mineralocorticoid) action.

In this way delta-1-dehydrocortisone (prednisone) and delta-1-dehydro-hydrocortisone (prednisolone) were born (Herzog *et al.*, 1955), and it was rapidly evident that these new substances (fig. 1) had a definite place in the treatment of most of those conditions which had responded favourably to cortisone and hydrocortisone (Bunim *et al.*, 1955). The advantages seemed likely to be:—

(a) That these new substances, being apparently some four to five times

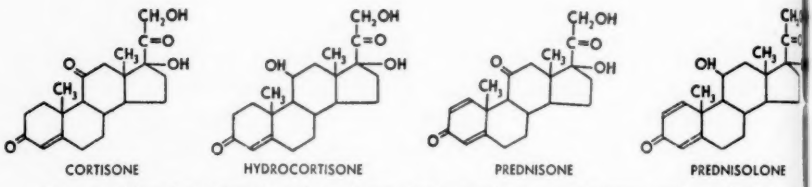

FIG. 1.—Chemical formulæ of cortisone, hydrocortisone, prednisone and prednisolone.

more potent than cortisone acetate as 'antirheumatic' agents, could be given in a much smaller dose.

(b) That the absence of marked mineralocorticoid action would be of benefit, particularly in patients with incipient or actual heart failure.

The hopes for the future were:—

(1) That undesirable 'side' effects would be less with prednisone and prednisolone than with their predecessors.

(2) That they would prove more effective and potent 'antirheumatic' agents.

(3) Even if these two hopes proved false, that by removing one undesirable effect, that of salt and water retention, these agents would still be an advance on their predecessors as anti-inflammatory agents in this respect alone.

Taking all these facts into consideration, and noting that a smaller dosage was needed, many patients were hopefully changed from cortisone or hydrocortisone to one of the newer compounds, for the expense was only slightly more per dose, and at least one undesirable effect seemed less likely to occur.

DOSAGE

In the assessment of any new drug in therapeutics the value of its effect as a therapeutic agent has to be weighed in the balance against its undesirable so-called side-effects. The latter, unfortunately, tend to appear some little time after the former, and the high wave of enthusiasm for many new therapeutic agents has been followed on most occasions in recent years by a secondary depression caused by seeing their dangerous and occasionally fatal toxic effects some months or years later. This 'wave and trough' sequence is caused to a large extent by the use of an initial dosage which,

spectacular in its initial therapeutic effect, is equally impressive in its later production of toxic sequelæ.

Hench and his colleagues, in 1949, demonstrated the effectiveness of cortisone in the first treated cases of rheumatoid arthritis with a dosage of 300 mg. on day one, 200 mg. on day two and a subsequent dosage of 100 mg. daily. The dramatic response which took place within forty-eight hours of starting treatment convinced all of us who saw these early cases that here was a most potent and effective new weapon. Had the initial dosage used been smaller the demonstration would have been less dramatic and the point as to clinical efficiency made less effectively. This or similar high dosage, used somewhat indiscriminately and against the advice of the original workers, produced throughout the United States a wide range of toxic reactions and occasional disasters, so that within a matter of months medical publications began to reflect the reverse side of the coin and in 1951 Derbes and Weiss published a small book on untoward reactions of cortisone and ACTH, giving 96 references.

Hydrocortisone is secreted by the human adrenals in amounts varying usually from 20 to 40 mg. daily under normal conditions. It is not surprising that continued higher dosage produces 'hypercortisonism' with occasionally unpleasant side-effects. For this reason, in this country today few workers ever exceed 75 mg. of cortisone acetate in the day-to-day suppressive treatment of chronic rheumatoid arthritis, and the original workers in the Mayo Clinic now use an even smaller dosage. The series of events seen here has been an initially high dosage demonstrating therapeutic effectiveness, followed by a high incidence of undesirable effects, resulting in reduced dosage with fewer side-effects and considerably less dramatic clinical improvement.

With prednisone and prednisolone exactly the same mistake appears to have been re-made. Introduced by Bunim *et al.* (1955) in the treatment of rheumatoid arthritis, the dosage used was usually $\frac{1}{3}$ to $\frac{1}{4}$ that of cortisone acetate. The initial therapeutic results were excellent and we (Hart, Clark and Golding, 1955) found that in a short-term study most patients preferred prednisone or prednisolone to cortisone in $\frac{1}{4}$ to $\frac{1}{5}$ the dose and benefited initially after the change to the newer substances. A continued study of these and other patients in the two years since then has demonstrated that in some cases the improvement is not maintained and some patients even benefit when replaced on cortisone.

Bunim's own recent figures are the most telling (Black, Yielding and Bunim, 1957). In 1956, six of 39 prednisone-treated patients died after a duration of therapy of six to eighteen months, the daily dose varying from 15 to 30 mg.; five had had cortisone or hydrocortisone previously. Three died of massive hæmorrhage, one from a duodenal ulcer, one from a double gastric ulcer and one from a ruptured liver hæmatoma due to vascular necrosis; one patient died of pneumococcal pneumonia and meningitis. On the evidence it seemed likely that four out of these six deaths could reasonably be attributed to therapy. In a series of 15 patients treated continuously with prednisone and observed for a period of two years these same workers reported that 14 showed facial rounding, 10 hirsutism, 10 cutaneous purpura or

ecchymosis, nine had epigastric pain, five had spontaneous fractures, four peptic ulceration and four mental changes. In their larger series of 39 patients, nine had fractures, most commonly of dorsal vertebræ, and four developed polyarteritis nodosa. They comment that the hazards of long-term prednisone therapy increase alarmingly when the daily dose exceeds 15 mg. At the 9th International Rheumatological Conference held in Toronto last June, Bunim gave his latest figures. Out of 49 treated patients 23 had suffered serious side-effects and he re-emphasized his point that long-term hazards increase greatly if dosage of prednisone is increased above 15 mg. daily. The average daily dose of prednisone when peptic ulceration developed was 20 mg.

He was followed in discussion by Engleman of San Francisco, who, using a more conservative dosage of 5 to 15 mg. (average dose 8 mg.), in two years had seen major undesirable effects in only nine of 36 patients (25 per cent.). In Engleman's series there were no cases of polyarteritis nodosa, four of peptic ulcer (11 per cent.), pathological fractures in 6 per cent. and only one death (from sepsis) attributable to therapy. Boland (1956a), on changing 109 patients from hydrocortisone to what would now be considered a slightly larger relative dose of prednisone, found that the incidence of gastric complaints simulating those due to peptic ulceration rose from 5.5 to 31 per cent. Kern, Clark and Lukens are quoted by Black, Yielding and Bunim (1957) as finding three of 14 patients treated on prednisone developing peptic ulceration with a daily dose of 20 mg. or more, whereas none of 54 patients developed ulcers when treatment was restricted to 15 mg. daily or less.

On the evidence now available it seems that the incidence of complications with prednisone, or prednisolone, for there seems little to choose between them, varies, as with cortisone or hydrocortisone, with the dosage, larger doses being accompanied, as might well be expected, by a higher incidence of complications. The same mistake of early overdosage was re-made here as it had been previously with cortisone. And this brings us to the next point. What are the equivalent effective therapeutic dosage levels of prednisone and prednisolone as compared with cortisone?

RELATIVE EFFECTIVENESS OF CORTISONE AND PREDNISONE

In the first report of the production of these new substances in the research laboratories of the Schering Corporation (Herzog *et al.*, 1955) the eosinophilic response in adrenalectomized mice is stated to be three to four times that to cortisone or hydrocortisone.

The enhanced glucocorticoid activity was confirmed by assays employing liver glycogen depletion in adrenalectomized rats and thymus involution in intact mice; again a 3-4:1 increase of activity was seen (Perlman and Tolksdorf, 1955). Kupperman and his colleagues (1955) compared the effect of various steroids on corticotrophin secretion in man; prednisone was less effective in suppressing features of the adrenogenital syndrome than 9-α-fluorohydrocortisone, but more so than hydrocortisone, cortisone being the weakest on a weight for weight basis. Holten and his colleagues (1957), in comparing the effect of cortisone and prednisone on intravenous glucose tolerance, found that 20 mg. of prednisone impaired tolerance to the same extent as 100 mg. of cortisone.

In human subjects Slaunwhite and Sandberg (1957) found that prednisolone injected intravenously disappears from the blood at the same rate as does hydrocortisone, but that it reached a concentration 50 per cent. higher in the blood. They found very low 17-ketosteroid excretion on prednisone therapy. Christy, Wallace and Jailer (1956) compared the effects of prednisone and cortisone in suppressing the response of the adrenal cortex to exogenous adrenocorticotrophin and found prednisone four times as effective as cortisone. Boland (1956b), comparing the relative antirheumatic potencies of prednisone and hydrocortisone, estimated the ratio to be approximately 4:1, and considered that prednisone and prednisolone were, for all practical purposes, interchangeable.

In our own series we have found the equivalent dose ratio of cortisone to prednisolone to be 5 or 6 to 1 and it is noteworthy that the tablet of cortisone acetate in common use contains 25 mg., that of prednisone or prednisolone 5 mg.; a 5:1 ratio. The acceptance of the correct dose ratio as 5-6:1 in all

Name	Manufacturer	Type of preparation	Contents
		PREDNISONE	
Asmacort	Roussel	Tablet	Prednisone 1.5 mg. Ephedrine hydrochloride 10 mg. Theophylline 80 mg. Phenobarbitone 10 mg.
Coactyl	Ward, Cassenne	Tablet	Prednisone 0.5 mg. Acetylsalicylic acid 300 mg. Aluminium hydroxide 160 mg. Magnesium trisilicate 30 mg.
Co-deltra	Merck, Sharp & Dohme	Tablet	Prednisone 5 mg. Magnesium trisilicate 50 mg. Dried aluminium hydroxide gel 300 mg.
Decortisyl	Roussel	Tablet	Prednisone 1 and 5 mg.
Deltacortone	Merck, Sharp & Dohme	Tablet	Prednisone 5 mg.
Deltalone	Ward, Cassenne	Tablet	Prednisone (buffered) 1 and 5 mg.
Di-adreson	Organon	Tablet	Prednisone 5 mg.
Ultracorten	Ciba	Tablet	Prednisone 1 and 5 mg.
		PREDNISONE ACETATE	
Delta-cortelan	Glaxo	Tablet	Prednisone acetate 1 and 5 mg.

TABLE I.—Proprietary preparations of prednisone.

those conditions in which these substances are used for their anti-inflammatory effect will be productive of fewer side-effects, and many of the admittedly common digestive upsets with prednisone and prednisolone will be diminished by taking this dose ratio as the correct one. The 3:1 or 4:1 ratio accepted by some of the earlier workers has been in part responsible for the higher incidence of side-effects with these newer compounds. The report of the joint committee of the Medical Research Council and Nuffield Foundation (1957), comparing cortisone and prednisone in the treatment of rheumatoid arthritis, came out in favour of the latter drug, but, once again, dosage was relatively higher, the ratio 1:3 being used. Not surprisingly, the incidence of side-effects and complications was higher in the prednisone-treated group.

PREPARATIONS AVAILABLE

Prednisone and prednisolone are available under a variety of names from different pharmaceutical firms (tables I, II), in oral tablets of two strengths, 1 and 5 mg.; the latter tablet is the one in more common use. The dosage must always be exactly stated; otherwise 'one tablet t.d.s.' may be taken by

the dispenser as being 3 or 15 mg. daily. The Ministry of Health, in 'Prescribers' Notes', asks doctors not to prescribe particular brands under the National Health Service, but to leave it to the chemist to supply any of the several very similar brands in stock, thus saving unnecessary delay. In recent months a variety of tablets has appeared in which small amounts of prednisolone are compounded with aspirin, antacids or tranquillizing agents.

Name	Manufacturer	Type of Preparation	Contents
		PREDNISOLONE	
Codelcortone	Merck, Sharp & Dohme	Tablet	Prednisolone 5 mg.
Co-hydeltra	Merck, Sharp & Dohme	Tablet	Prednisolone 5 mg. Magnesium trisilicate 50 mg. Dried aluminium hydroxide gel 300 mg.
Cordex	Upjohn	Tablet	Prednisolone 0.5 mg. Acetylsalicylic acid 300 mg.
Cordex forte	Upjohn	Tablet	Prednisolone 1.5 mg. Acetylsalicylic acid 300 mg.
Deltacortril	Pfizer	Tablet	Prednisolone 1 and 5 mg.
Delta-cortef	Upjohn	Tablet	Prednisolone 5 mg.
Deltalglycortril	Pfizer	Tablet	Prednisolone 0.5 mg. Acetylsalicylic acid 300 mg.
Deltastab	Boots	Tablet	Prednisolone 1 and 5 mg.
Deltastab-B	Boots	Tablet	Prednisolone 5 mg. Aluminium hydroxide 300 mg. Magnesium trisilicate 50 mg.
Di-adreson-F	Organon	Tablet	Prednisolone 5 mg.
Hydeltracin	Merck, Sharp & Dohme	Lotion	Prednisolone 0.5% Neomycin sulphate 0.5%
Hydrodeltalone	Ward, Cassenne	Tablet	Prednisolone 1 and 5 mg.
Hydrodeltalone ointment	Ward, Cassenne	Ointment	Prednisolone 0.5% Neomycin ointment 0.5%
Precortisyl	Roussel	Tablet	Prednisolone 1 and 5 mg.
Ultracorten-B	Ciba	Tablet	Prednisolone 1 and 5 mg.
		PREDNISOLONE ESTERS	
Delta-ef-cortelan	Glaxo	Tablet	Prednisolone acetate 1 and 5 mg.
Hydrodeltalone	Ward, Cassenne	Intra-articular injection Eye ointment Eye-drops	Prednisolone acetate 25 mg. per ml. Prednisolone acetate 0.25% Prednisolone acetate 0.25%
Precortisyl injectable	Roussel	Solution	Prednisolone acetate 25 mg. per ml.
Ultracortenol	Ciba	Microcrystalline suspension for intra-articular injection	Prednisolone trimethylacetate 10 mg. per ml.
Ultracortenol with bradosol cream	Ciba	Cream	Prednisolone trimethylacetate 0.5% Domiphen bromide 0.05%

TABLE II.—Proprietary preparations of prednisolone.

There seems little reason for these compound tablets, for they often lead to over- or under-dosage with one or other substance, and it is more accurate to prescribe the two substances independently. Most patients with rheumatoid arthritis take a form of acetylsalicylic acid which they have found from hard experience suits them best; it is preferable for them to continue with such tablets as required in addition to the prescribed dose of prednisone or prednisolone.

There are also compound tablets for asthmatics, containing ephedrine, theophylline and phenobarbitone in addition to prednisone; nasal drops containing soframycin and phenylephrine in addition to prednisolone; creams containing prednisolone trimethyl acetate and 'bradosol', lotions containing prednisolone and neomycin and so on. Time will perhaps show what advantages these various compounds have over simpler preparations.

GENERAL USES OF PREDNISONE AND PREDNISOLONE

For practical purposes prednisone and prednisolone are best considered as having exactly the same action as cortisone and hydrocortisone, but with less salt-retaining, potassium-losing effect. It seems likely that, milligram for milligram, salt retention is similar in all these substances, but the delta compounds, being given in much smaller dosage, are less likely to produce this effect. Nevertheless, pushed to high level, salt and water retention and potassium loss, sometimes with the development of hypertension, do occur if dosage be high enough. In their original report (1955) Bunim and his colleagues report that in two rheumatoid patients 30 mg. of prednisone a day for twelve days had no effect on sodium, potassium or nitrogen balance, whereas 50 mg. daily for twenty-four days produced a definite negative nitrogen balance in one case. With dosage of prednisone and prednisolone kept at the 'safe' level of 15 mg. daily, or less, electrolyte and nitrogen imbalance are extremely unlikely to occur. For this reason, in incipient or actual heart failure the delta groups are to be preferred, and in many other conditions, on changing from cortisone to the delta compounds, a definite diuresis is noted, showing that some water loading had occurred with the first drug.

In the majority of cases, however, this property is not of major importance, and prednisone and prednisolone are given in all those conditions in which cortisone or hydrocortisone is used essentially for its 'antirheumatic' or anti-inflammatory effect: rheumatoid arthritis, rheumatic fever, status asthmaticus, ulcerative colitis, allergic disorders, leukæmia, hæmolytic anæmia, acute gout and so on. In adrenal deficiency states, however, because of their diminished salt-retaining action, prednisone and prednisolone are not to be preferred to cortisone and hydrocortisone, and these latter substances, together with the occasional use of a stronger salt-retaining substance, such as deoxycortone or fludrocortisone, are to be preferred. When large doses of steroid are necessary, as in severe status asthmaticus,

and in severely ill cases of polyarteritis nodosa or disseminated lupus erythematosus, in which the usual dosage gives insufficient control, and in cases of metastatic carcinomatosis and leukæmia in which large doses are also employed for their suppressive action on the malignant process, prednisone and prednisolone are to be preferred to cortisone or hydrocortisone because of their lessened mineralocorticoid action.

In them we have two new compounds which do much the same things clinically as cortisone or hydrocortisone, with much the same range of side-effects if dosage be too high. Given in approximately one-fifth the dosage and kept at safe levels—at or below 15 mg. daily—salt and water loading and potassium depletion do not occur. Prednisone and prednisolone are therefore extremely useful in a wide range of disorders and are a most helpful addition to our steroid therapeutic armamentarium.

LOCAL USE

Prednisolone, like hydrocortisone, may be used locally in *rheumatoid arthritis* by intra-articular injection; prednisone, like cortisone, is unsatisfactory by this route. A slow-acting form, prednisolone trimethylacetate, is now available with an action similar to hydrocortisone tertiary butyl acetate. Whether these long-acting forms are significantly superior to the original hydrocortisone given intra-articularly remains unproven in this country, although some workers' clinical impressions are in their favour; there are so many variables in the response of affected joints to treatment that accurate assessment is extremely difficult. In general it seems that most clinics find little advantage in using prednisolone rather than hydrocortisone for injection into a joint, although some prefer the long-acting forms of either to the short. It is of interest to note that the intra-articular dose of prednisolone appears to be very similar to that of hydrocortisone; the 1:5 dose ratio does not apply here.

In the *eye*, cortisone, hydrocortisone, prednisone and prednisolone may all be used as local agents. There seems little to choose here, although again, there are claims that the delta compounds are superior to their predecessors. The same difficulty in assessing results applies here as it does with intra-articular injections.

Applied to the *skin* prednisolone is used as a lotion and as an ointment or 'cream'. Some preparations are available which combine an antibiotic with prednisolone. Again, there seems little to choose here between the delta compound and its predecessors.

Godfrey, Maunsell and Pearson (1957) used prednisolone snuff in *hay fever* and concluded that, as compared with a control inert substance, it was of considerable value in the control of symptoms. Prednisolone nasal drops alone or in different combinations have been used and are available.

On reviewing the different publications and brochures regarding the local use of prednisolone, it is apparent that, as the one main advantage of the delta compounds, i.e. their reduced mineralocorticoid or salt-retaining

action, does not apply in local treatment, there is little rationale in preferring them to their predecessors in this field of therapy.

METABOLISM OF PREDNISONE AND PREDNISOLONE

Among the large number of reports on the clinical uses of these substances there are very few on what happens to these substances in the body. Gray and his colleagues (1956) investigated the steroids excreted by patients receiving prednisone or prednisolone by mouth. The two compounds present in the largest amounts were isolated and identified as prednisone and prednisolone. There was no evidence of conversion in the body to cortisone or hydrocortisone or their derivatives. Their investigations suggested that the metabolism of prednisone was in part by reduction of its 11-ketone group to an 11-hydroxy group; of prednisolone by oxidation of its 11-hydroxy group to an 11-ketone group. These two compounds were therefore metabolically convertible. Reduction of the 20-ketone group could occur in both compounds. Unlike what is found with the older compounds, no trace of tetrahydrocortisone or tetrahydrohydrocortisone was found.

Prednisone and prednisolone are known to exert a powerful suppressing action on corticotrophin production in the anterior pituitary, resulting in adrenocortical hypoplasia and reduced 17-ketosteroids and 17-hydroxysteroids in the urine.

Vermeulen (1957) studied the 17-ketosteroids excreted in a patient who had undergone bilateral oöphorectomy and total adrenalectomy for metastasizing breast carcinoma. The patient was given 80 mg. of prednisolone daily; less than 2 per cent. could be recovered as 17-ketosteroids. He states: 'The urinary metabolites of prednisone and prednisolone so far known represent only a small proportion of the administered dose, and we are still ignorant of what happens to the bulk of the administered dose'.

In the past two years some workers have doubted whether prednisone or prednisolone given orally have the same action or whether they are equally potent. Most workers, ourselves included, have considered them freely interchangeable and for all practical purposes identical. The work of Gray and his colleagues helps to explain the similarity of action and virtual therapeutic identity of the two substances when given by mouth.

SUMMARY AND CONCLUSIONS

(1) Prednisone and prednisolone are metabolically interchangeable. Given by mouth their therapeutic effect appears identical.

(2) Used as anti-inflammatory or 'antirheumatic' substances they should be given in one-fifth to one-sixth the dose of cortisone. At this equivalent dosage the effects, therapeutic and toxic, are those seen with cortisone. They are used in the treatment of the same conditions as cortisone: status asthmaticus, rheumatoid arthritis, ulcerative colitis, allergic disorders and a host of others.

(3) Their diminished salt- and water-retaining actions make prednisone and prednisolone preferable to cortisone in all conditions where salt and water retention are undesirable; this includes all conditions in which these

substances are used for their anti-inflammatory or 'antirheumatic' action, particularly if high dosage is needed. In adrenal replacement therapy, as after adrenalectomy or in Addison's disease, this property makes these substances less suitable than cortisone or hydrocortisone, which are still to be preferred in the treatment of these conditions.

(4) Although prednisone and prednisolone have been considered more productive of peptic ulceration and indigestion generally than cortisone, it seems likely that this was largely the result of a relatively higher dosage being used. The same fact probably accounts for their reputed greater efficiency in a variety of diseases.

(5) When high dosage is needed to suppress neoplastic disease, as in some cases of metastatic carcinomatosis and in leukæmia, the new compounds are preferable to cortisone for the reason given above.

(6) Used locally in the eye, on the skin or in a joint, prednisolone appears to give no better results than hydrocortisone. Nevertheless, it is useful to have an alternative in this as in other fields of therapy, for individual patients will often respond better to one substance than to another.

(7) Dosage of prednisone or prednisolone, if to be continued for longer periods than fourteen days, should not exceed 15 mg. daily by mouth. Although higher dosage may be necessary in conditions dangerous to life, an increased incidence of toxic effects identical with those caused by cortisone may be seen when this dose is exceeded. In day-to-day treatment the correct dose, as with cortisone, is the lowest which produces reasonable, but not necessarily complete, suppression of distressing symptoms.

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CORTICOTROPHIN

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Corticotrophin is the official name for the hormone formed by the anterior lobe of the pituitary gland which is responsible for the secretory activity of the adrenal cortex. The earlier descriptive name of adrenocorticotrophin (ACTH) is still commonly used as a synonym.

The place of corticotrophin in research and therapeutics has not yet been settled. From the point of view of therapy, corticotrophin has been largely replaced in recent years by synthetic adrenocortical steroids such as cortisone and hydrocortisone, and their analogues, prednisone and prednisolone. In the United Kingdom the hormone is still distributed by the Ministry of Health for clinical use in hospitals only, but it is doubtful whether this has seriously limited its contribution to the control of disease.

NATURE AND SOURCES

This hormone, like the others formed in the anterior pituitary, was thought to be a protein, but it has now been shown to be a polypeptide consisting of thirty-nine amino-acids linked together (Bell *et al.*, 1955; Li *et al.*, 1955). These two groups of workers have shown that corticotrophin prepared from pigs' pituitaries is not identical with that from sheep. Whilst the chemical structure of human corticotrophin has not yet been determined, it seems possible that some of the anomalies in the responses given by patients treated with preparations from different animal sources might be due to the administration of a foreign polypeptide, and to contaminating proteins obtained from a species other than man. For some time corticotrophin was thought to be identical with the melanocyte-stimulating hormone (intermedin), but recent evidence indicates that, although the two share many biological and some chemical properties, they are not chemically identical.

The chemical nature of corticotrophin and its rapid destruction by the proteolytic enzymes of the intestine mean that it must always be administered by a parenteral route. Further, even after intramuscular or intravenous injection the hormone is inactivated very rapidly, and special precautions are required to ensure its continued effectiveness.

ACTION

When corticotrophin is administered to man the healthy adrenal cortex responds by an increased output of many of the thirty or more steroids known to occur in that gland.

Several factors determine the nature and extent of the secretory response

by the adrenal cortex. Prunty (1956a) has summarized these as follows:—

Factors affecting the secretory response to corticotrophin:—

(1) The potency of the corticotrophin preparation used, there being a wide divergence between the potency shown on the label, and that found on intramuscular injection.

(2) The variation between patients in the responsiveness of the adrenal cortex to the same dose of the same preparation.

(3) The changing response to daily injections, increasing to a maximum after several days.

(4) The difference between patients in response to relatively small alterations in dosage.

(5) The diminishing responsiveness of some patients to the continued administration of corticotrophin.

It is scarcely necessary to add that the type of preparation, dose, route, and frequency or rate of administration will all affect the response.

Estimations of corticotrophin in body fluids such as blood and urine unfortunately are still not sufficiently reliable to be of much value in the study of disease (Loraine, 1957a). The hormone has been detected most readily in the blood of patients with Addison's disease, bilateral adrenal hyperplasia and after bilateral adrenalectomy. That it can no longer be detected in these conditions during treatment with cortisone (Sayers, 1955) and hydrocortisone (Bethune *et al.*, 1957) supports the current concept of a reciprocal relationship between the concentration of circulating corticotrophin and adrenocortical hormones, and would account for the atrophy of the adrenal cortex which is so striking and important a feature of patients in whom cortisone and its analogues have been used for any considerable period.

THE ASSESSMENT OF THE RESPONSE TO CORTICOTROPHIN

In the management of disease it is often only possible for the clinician to observe the effect of the treatment on the manifestations of the disease, and then to weigh the probability of the response being due to the treatment. Since the secretory response to corticotrophin is so variable, and since the therapeutic response depends upon the amount of hormones produced by the adrenal cortex, it is important that whenever possible this adrenocortical response should be measured. Because of the relative complexity of the methods for estimating steroid hormones in body fluids, usually in blood or urine, and the lack of reliability of many of the methods available, indirect indices of adrenocortical response have been widely used. Such methods have included changes in the eosinophil count in the peripheral blood, changes in the ratio of uric acid to creatinine in urine, changes in capillary resistance, and changes in urinary electrolyte excretion. These indirect tests, however, are all of limited value.

When facilities are available or can be created, one or more of the many methods for estimating the steroids of adrenocortical origin in blood or

urine should be used to assess the response to corticotrophin.

Prunty (1956b) described a number of tests which he and his colleagues have used for several years to measure this response. Obviously the most suitable test for particular circumstances will vary. For example, in treating a condition depending for a clinical response upon the amount of hydrocortisone secreted by the adrenals, one of the methods which measures the group of corticosteroids including hydrocortisone and its metabolites would be appropriate. In the diagnosis of Addison's disease, in which the amount of steroid to be expected will be small, the most sensitive method available should be used. In the assessment of the completeness of adrenalectomy, particularly when this has been performed for malignant disease of the breast, and when the success of the operation in controlling the disease is believed to be related to the removal of the sources of sex hormones such as the œstrogens and progesterone, appropriate methods for measuring their metabolites should be applied (Brown, 1955; Klopper *et al.*, 1955). The value of any method used will depend in large measure upon its *reliability*. Further discussion of this and the many methods available is beyond the scope of this article; both subjects have recently been comprehensively reviewed by Loraine (1957b).

PREPARATIONS AND DOSAGE

The material distributed to hospitals in the United Kingdom is produced by three firms from the pituitaries of domestic animals. Two types of preparation are available: a soluble form which may be given by intramuscular or subcutaneous injection, and a form intended for intramuscular injection but suspended in a medium designed to delay its absorption and so to prolong its action. Some preparations of the soluble form are suitable for intravenous use but, in view of the known dangers of the intravenous administration of foreign protein, only preparations marked as suitable for intravenous use should be given by this route, and then only under immediate supervision.

In 1950, the World Health Organization established an international standard, and the international unit (I.U.) was defined as the activity present in 1 mg. of this material. The British and United States Pharmacopœial standards are identical. Later and purer preparations of corticotrophin have been much more active, and the purest, which were used to establish the structure of the material, assayed at about 100 I.U. per mg. Doses should always be expressed in terms of I.U., certainly until the pure hormone is generally available.

Jenkins *et al.* (1955) pointed out that the slow-absorption preparation, 'ACTH gel', had been re-standardized in terms of 'commercial' or 'clinical' units, 3 clinical units being equivalent to 1 I.U. This was done because the manufacturers found that a single injection of 13 to 14 I.U. of 'ACTH gel' produced a similar clinical effect to that elicited by the intermittent intramuscular injection of 40 I.U. of a soluble preparation.

The soluble preparation of corticotrophin is dispensed in rubber-capped bottles, each containing 10, 15, 25 or 40 I.U. Immediately before use this should be dissolved in isotonic saline or the solvent provided. Once dissolved, it loses its activity fairly rapidly, even if refrigerated.

The slowly absorbed or depot preparations are as follows:—

(1) 'Acthar gel H.P.' (Armour), a mixture of corticotrophin in gelatin.

(2) 'Cortrophin Z' (Organon), prepared by the adsorption of corticotrophin upon a zinc salt in fine aqueous suspension.

(3) 'Cortico-Depot' (Crookes), a suspension of zinc protamine and corticotrophin.

These must be given by intramuscular injection, never intravenously. They have the great advantage of being slowly released, absorbed and inactivated, so that by using single or twice-daily injections, almost continuous stimulation of the adrenals may be maintained. The soluble preparations are rapidly inactivated at the site of injection and, unless given intravenously, the stimulus to the adrenals will only be intermittent.

The *doses* of corticotrophin to be given depend entirely upon the purpose for which the drug is being used. For *temporary maximal stimulation* one of the following procedures would be appropriate:—

(1) A continuous intravenous infusion of a soluble preparation of corticotrophin in isotonic saline or glucose, at the rate of 20 I.U. eight-hourly.
(2) 'Acthar gel H.P.', the 'clinical equivalent' of 60 I.U. every twelve hours.
(3) 'Cortrophin Z', 20 I.U. daily.
(4) 'Cortico-Depot', 40 I.U. twice daily.

These figures are to be regarded as maxima beyond which no increase in response need be anticipated. Administration at this rate should not be maintained for more than a few days.

Moderate adrenocortical stimulation will be provided by considerably smaller doses as follows:—

(1) 'Acthar gel H.P.', 40 'clinical' units once daily.
(2) 'Cortrophin Z', 20 I.U. on alternate days.
(3) 'Cortico-Depot', 20 I.U. daily.

Smaller doses may occasionally be called for; requirements are usually determined by trial and error as the least amount that will maintain the clinical effect sought. The intravenous method is only necessary and justified when the fullest possible response is essential.

CLINICAL APPLICATION OF CORTICOTROPHIN

In November 1955, *The Practitioner* published a symposium devoted to cortisone and corticotrophin, and most of the applications of these drugs were then described. The necessity for intravenous infusions or repeated intramuscular injections of corticotrophin, in contrast to the convenience of the oral use of steroids, naturally means that when the choice might otherwise be immaterial, or even slightly weighted in favour of corticotrophin, the oral preparation is preferred.

A further potential disadvantage of corticotrophin lies in the non-specific nature of the response by the adrenal cortex. With the newer corticosteroid analogues, such as prednisone, prednisolone and fludrocortisone, relatively specific effects are possible. Thus, prednisolone will suppress the manifestations of rheumatoid arthritis or asthma with the minimum of side-effects, such as gain in weight, sodium retention and potassium depletion. Fludrocortisone, even in small doses, causes sodium retention and enhances potassium excretion without affecting carbohydrate metabolism or reproducing many of the other effects of cortisone. Effective corticotrophin therapy, however, especially if vigorous and prolonged, may be marked by numerous side-effects attributable to the secretion of the corticosteroids,

hydrocortisone and cortisone, androgens, and aldosterone (Muller *et al.*, 1956). It has also been shown that the infusion of corticotrophin is followed by an increase in the excretion of pregnanediol in the urine, probably derived from progesterone (Klopper *et al.*, 1957). The excretion of œstrone, œstradiol-17β and œstriol, three of the œstrogens known to occur in human urine, is also increased in this way (Brown and Strong, 1957). Obviously, many of these steroids are unlikely to be associated with the pharmacological response sought, and may lead to undesirable side-effects.

For these and other reasons, the demand for corticotrophin in the control of disease appears to have declined relative to the increased use of cortisone and its new analogues. The most serious single limitation of the commercial preparations of corticotrophin available lies in the gross variations in their biological activity (Prunty, 1956b) and, until much purer and more consistently active preparations become available, the use of the drug is unlikely to extend or even to be maintained in therapeutics. A slight preference has sometimes been expressed for corticotrophin, rather than adrenocortical steroids or their analogues, in the treatment of specific diseases.

For example, Nicholson, writing in 1955, took this view in relation to asthma, and Kirsner *et al.* (1957), in discussing the treatment of ulcerative colitis, were more definitely in favour of corticotrophin. In their view the 'spectrum of hormones' secreted was to be preferred to the administration of a single steroid.

On the other hand, many would agree with the view of Hill (1957), who remarked, in relation to the treatment of disseminated lupus erythematosus, that the side-effects of corticotrophin outweigh its usefulness.

It is clear that in many diseases a controlled comparison between the effects of treatment with corticotrophin or a single steroid has not yet been made.

The indications for the use of corticotrophin fall into two groups, namely —(1) The treatment of certain specific diseases. (2) The investigation of adrenocortical function.

THE TREATMENT OF SPECIFIC DISEASES

Two important considerations appear to determine the choice of corticotrophin in the treatment of disease. In the first place, is there any evidence that adrenocortical hormones have any part to play in the management of the condition, and secondly, is corticotrophin to be preferred to cortisone, and the newer steroid analogues? There is general support for the use of adrenocortical hormone therapy in a wide variety of conditions, with the reservation that in most of these, control only, rather than cure, of the disease can be expected. In this respect there is little to add to the recommendations offered in numerous reviews and many textbooks (e.g. *The Practitioner* symposium on Cortisone and Corticotrophin, November 1955; Bayliss, 1955; Dunlop, 1955; Goodman and Gilman, 1955).

It may be argued that the use of corticotrophin and the increased production of endogenous adrenocortical hormones are more physiological than

the administration of relatively large quantities of a single steroid. Whilst this is true, there is no evidence that the majority of the diseases which respond to either form of treatment are due to inadequate function in either the pituitary or the adrenal cortex. The action of these drugs should be regarded as pharmacological rather than physiological; they disturb rather than restore the normal balance between the pituitary, the adrenals, and their secretions.

The resuscitation of the suppressed adrenal.—In 1950, Sayers reviewed the evidence bearing on the relationship between corticotrophin and corticosteroid secretion. Three possibilities were considered: (a) that the rate of secretion of corticotrophin is determined by the concentration of circulating adrenocortical hormones, (b) that the hypothalamus produces a substance which in turn stimulates the production of corticotrophin by the pituitary, and (c) that adrenaline might play some part, either by direct stimulation of the adrenal cortex or by stimulating secretion of corticotrophin by the pituitary.

Although the significance of the two latter mechanisms may be problematical, the importance of the former is unquestionable. It is now widely recognized that prolonged treatment with cortisone and its analogues may be followed by adrenocortical insufficiency. This becomes particularly important, for example, in the case of patients who have been treated with cortisone for ulcerative colitis, when they are subsequently submitted to ileostomy and colectomy (Salassa *et al.*, 1953; Hayes, 1956; Slaney and Brooke, 1957). The assumption is often made that the adrenal insufficiency sometimes found during and after operations in these circumstances is due to adrenocortical atrophy, and that it can be prevented by treatment with corticotrophin. This would appear to be partly correct. Bennett (1953), however, has shown that in patients treated with corticotrophin or cortisone characteristic changes are found in the basophil cells of the pituitary, of a type suggesting that these cells are unlikely to function properly. It seems probable that this type of induced adrenocortical insufficiency is due primarily to the effect of previous hormone treatment on the pituitary. It follows therefore that, although adrenocortical atrophy may be corrected by treatment with corticotrophin before subsequent operation, it is very likely that some of these patients, left to their own resources, will still be unable to meet the demands of operation by an appropriate adrenocortical response. Unless therefore treatment with corticotrophin is continued throughout the period of operation and subsequent early convalescence, then all these patients should be regarded as possible candidates for acute adrenal insufficiency. Provided this danger is constantly borne in mind, it is probably unnecessary to treat all patients of this type with corticotrophin. Until some adequate method is devised of predicting the patient's capacity to produce an appropriate adrenocortical response to operation, treatment for acute adrenal insufficiency should always be immediately available in the circumstances described.

THE INVESTIGATION OF ADRENOCORTICAL FUNCTION

Whilst the use of corticotrophin in therapeutics has become more restricted, its place in the diagnosis of adrenocortical disorders is firmly established.

Adrenal insufficiency.—This may take the form of Addison's disease, or may be a component of the syndrome of hypopituitarism: i.e. secondary adrenal insufficiency.

A number of indirect tests has been devised to demonstrate the effects of an inadequate supply of adrenocortical secretion; for example, the well-known Kepler test (Robinson, Power and Kepler, 1941). All these indirect tests may occasionally be misleading. The direct measurement of corticosteroids in blood and urine has already been discussed (p. 42).

Jenkins *et al.* (1955) and Prunty (1956b) described their extensive experience of the value and limitations of corticotrophin in the diagnosis of adrenal insufficiency. Two criteria of response by the adrenal cortex to corticotrophin are widely used: the decrease in the number of circulating eosinophils, and the rise in the urinary excretion of adrenocortical steroids. Bishop (1955) described in detail two of the methods of using corticotrophin in this context, and emphasized the lack of a widely acceptable simple method of measuring the adrenocortical steroid response. It is clear that the estimation of 17-ketosteroids, one of the earliest standard measures of adrenocortical function, can now be regarded as only of very limited value for this purpose.

At the present time two of the most useful and reliable tests for this type of work are those for *17-ketogenic steroids* described by Norymberski *et al.* (1953), and for *total 17-hydroxycorticosteroids* described by Appleby *et al.* (1955).

After bilateral adrenalectomy.—This operation has been widely practised since it was first introduced by Huggins and Bergenstal (1952) for the control of recurrent and metastatic mammary and prostatic carcinoma. The mechanism responsible for the effect of the operation has been generally assumed to be the removal of the source of adrenal sex hormones. It is often assumed, too, that the success or failure of operation might be related to the success or failure of the surgeon in removing all adrenocortical tissue, aberrant or otherwise. To test for evidence of residual tissue capable of producing adrenocortical steroids, corticotrophin has been given intravenously. Failure to increase the excretion of œstrogens, pregnanediol and 17-ketosteroids in this way was taken to mean that the small amounts of these steroids found in the urine of patients after adrenalectomy and oöphorectomy were not derived from adrenocortical tissue (Strong *et al.*, 1956).

The distinction between adrenal hyperplasia and tumour.—At one time it was believed that adrenocortical tumours secreted autonomously, and that their failure to respond to the administration of corticotrophin would help to distinguish patients with benign and malignant adrenocortical tumours from those with simple hyperplasia (Laidlaw *et al.*, 1955). Patients in the second group were usually found to show a brisk response to the injection of corticotrophin. Ross and Thorn (1957) have recently pointed out that these earlier hopes have not been confirmed, and Prunty (1956b) has also described a rise in the excretion of 17-ketogenic steroids and 17-ketosteroids in a patient with an adrenal carcinoma who was given corticotrophin.

Although corticotrophin may provide useful information in this type of

patient, it is unfortunate that the technique cannot be relied upon to distinguish between adrenal tumours and hyperplasia.

DANGERS AND CONTRAINDICATIONS

Wayne (1955) reviewed this aspect of the use of corticotrophin, and concluded that when the indications for the drug were sufficiently pressing, its use need rarely be excluded. Generally speaking, complications are more likely to occur with the larger doses, especially when treatment is prolonged. The *weakness and depression* associated with abrupt *withdrawal* of the drug may be avoided by always reducing the dose of the drug gradually. *Sensitivity reactions* due to the nature of the hormone itself or to contaminating proteins are rare with the purer preparations. They may still occur occasionally with the existing commercial preparations, and are most likely to occur when the drug is being used in patients with untreated adrenal insufficiency, especially when the drug is being given by intravenous infusion.

Mental disturbances have long been recognized as associated with adrenal disorders, both insufficiency and hyperfunction. Some caution is therefore required in managing patients with mental changes who need corticotrophin, and patients receiving corticotrophin who develop mental symptoms. Ritchie (1956) concludes that, whilst psychoses may be precipitated by corticotrophin, their occurrence cannot be predicted, nor can they be reversed by withdrawing the drug.

Bleeding and perforation of peptic ulcers occur sufficiently often for these two complications to be regarded as potential hazards of corticotrophin therapy. Many of the symptoms usually associated may be masked when intensive treatment is being given. *The delay in healing of wounds*, demonstrated experimentally in the early days of the use of adrenocortical hormones, has not proved to be a problem with more extensive experience of these drugs. *Increased susceptibility to infection* which follows hormone therapy is largely due to suppression of the normal protective inflammatory response, and in severe infections such as pneumonia or tuberculosis, existing dangers may be enhanced by corticotrophin. On the other hand, provided adequate antibiotics or chemotherapy are given, these risks should never prevent a patient requiring hormone therapy from being treated.

Modification of carbohydrate metabolism by these hormones may increase the requirements of insulin of *diabetic patients*, or might even lead occasionally to the recognition of a latent diabetic. Many of the features of *Cushing's syndrome*, including glycosuria, are liable to appear in patients undergoing intensive treatment with corticotrophin for long periods, but are the less likely to occur the shorter the treatment and the more carefully the dose is restricted to the minimum requirements for the control of the condition being treated. *Thrombo-embolic complications* of corticotrophin therapy have been reported (Fazlullah, 1956) and a possible mechanism is suggested in the inhibition of clot lysis demonstrated by Kwaan and McFadzean (1956).

The implications of the suppressive action of the adrenocortical hormones

on the pituitary have already been discussed. When hormone therapy is ultimately withdrawn some patients may be expected to respond abnormally to operation or indeed to any situation which involves increased adrenocortical activity.

SUMMARY AND CONCLUSIONS

The nature, sources and action of corticotrophin are reviewed briefly.

Some of the factors affecting the response of the adrenal cortex are discussed. The most important of these is the variable potency of the relatively crude preparations of corticotrophin available for clinical use.

Methods of assessing the response to the hormone, and the limited clinical indications for its use are described. There are few conditions in which steroid therapy would not be equally or more effective, and the outstanding indication for corticotrophin is in the diagnosis of adrenocortical disorders.

Few of the dangers of using the drug are likely to interfere with its limited applications.

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THYROID HORMONE THERAPY

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An adequate supply of thyroid hormone is not absolutely essential to life, but it is necessary for normal growth and development and for the maintenance of good health. The function of the thyroid gland is to extract iodine from the blood and bind it to protein, thus forming thyroglobulin. This is stored in the gland and, according to bodily demands, thyroxine is liberated by enzyme action and discharged into the bloodstream. Thyroxine enters the body cells and, by further enzyme action, is deiodinated to triiodothyronine which is thus the ultimate thyroid product.

The release of thyroxine from the thyroid gland into the bloodstream is governed by T.S.H. (thyroid-stimulating hormone or thyrotrophin) which is produced by the anterior lobe of the pituitary. This process is variable and reciprocal in that a low blood level of thyroxine will stimulate T.S.H. output and a high level will diminish it. The reason why thyroid substances are active when given by mouth is probably because the gland was not originally endocrine, but secreted directly into the mouth. Thus, in amphioxus a thyroid-like organ communicates directly with the alimentary tube, whilst in man the thyroglossal duct and foramen cæcum of the tongue are vestiges of a similar system which occasionally persist as thyroglossal cysts or a lingual thyroid. Thyroid substances therefore have an advantage over many other endocrine gland hormones by being active when given orally, but this very simplicity of administration should not encourage indiscriminate therapy.

DEVELOPMENT OF THYROID THERAPY

Thyroid.—Some eighty years ago—in 1873—Sir William Gull, physician to Guy's Hospital, described myxœdema under the title of 'A cretinoid state supervening in adult life in women'. He referred to the article by Hilton Fagge, who had described cretinism in 1871 and had speculated upon the possibility of the condition arising in adult life. Gull evidently took his cue from this report and suggested thyroid disease as the cause of the adult disorder. By thus drawing attention to the clinical evidence favouring thyroid deficiency in myxœdema Gull stimulated others to lay the foundations of clinical endocrinology by taking the first steps in thyroid replacement therapy. Within a few years thyroid grafting operations had been attempted and injections of sheep's thyroid had been given before it was realized that raw or lightly cooked sheep's thyroid was effective by mouth. Finally, Murray, in 1891, initiated the first successful treatment of a case of myxœdema with a glycerinated extract of sheep's thyroid. Shortly after-

wards dried thyroid, or thyroideum siccum, was produced and this remains the standard preparation in the *British Pharmacopœia* today.

Thyroxine.—The active principle in thyroid extract was isolated by Kendall in 1915 and named thyroxine. This was synthesized by Harington and Barger in 1927 in the racemic form and later work showed that the lævorotatory form (*l*-thyroxine) was some 8 to 10 times more potent than *d*-thyroxine which had little activity.

Triiodothyronine.—Doubts had always existed, however, as to whether thyroxine was the true or ultimate active thyroid substance. Thus it was relatively insoluble, there was an appreciable time-lag after administration before its action became manifest, and the activity of a known quantity of thyroid extract appeared to exceed that of its thyroxine content. It was not until 1952 that Gross and Pitt-Rivers clarified the position by isolating from human plasma a substance named triiodothyronine. This has since been synthesized and shown to be some three times as potent as thyroxine. It appears that thyroxine (tetraiodothyronine) is deiodinated in the body cells to triiodothyronine which exerts the physiological action of thyroid hormone.

Thyroid therapy has thus advanced a long way in eighty years, owing to the achievements of research workers in isolating and synthesizing the active principles. We now have thyroid, thyroxine and triiodothyronine for clinical use. Each has the same action, but differs from the others in potency and speed of action. This must not imply that the newest and most potent is therefore better than the older and slower-acting substances. Indeed, like motor cars, the latest and fastest models are not necessarily the best and safest for everyday use.

PHYSIOLOGICAL CHARACTERISTICS OF THYROID HORMONE

Thyroid hormone, in brief, is responsible for maintaining the metabolic rate of bodily processes and it is largely concerned with proper growth and development. It acts directly upon tissue cells and regulates their oxidation processes and so their oxygen consumption. Its action upon growth is probably concerned more with differentiation of tissues than with actual increase in size. Its effect is ultimately exerted with that of the pituitary growth hormone, but is probably independent of it. Thyroid hormone influences carbohydrate metabolism by promoting the release of glycogen from the liver and accelerating the oxidation of carbohydrate by the tissues. Apart from the reciprocal relationship with the anterior pituitary whereby the output of T.S.H. is balanced against the circulating level of thyroid hormone, there is no intimate or direct linkage with other endocrine glands if we except the effects mediated by alterations in the general level of bodily metabolism.

The physiological effects of thyroid, thyroxine and triiodothyronine differ for practical purposes only in the speed and intensity of their actions. If the crude thyroid substance is given by mouth the body has to

break it down ultimately to triiodothyronine before an effect is produced. But if thyroxine, or triiodothyronine itself, is given the effect is produced more quickly, and with a correspondingly smaller dose.

THERAPEUTIC CHARACTERISTICS OF THYROID HORMONE

Thyroid B.P. (*syn.* Thyroideum, thyroideum siccum, dry thyroid, thyroid extract, thyroid gland) is prepared from the thyroids of oxen, sheep or pigs by drying, extraction of fat and powdering. The residue is mixed with sufficient lactose to bring it to the pharmacopœial standard of 0.1 per cent. of iodine in combination as thyroxine. The powder, or tablets made from it, must be kept cool and dry. The official dose is ½ to 4 grains (30 to 250 mg.) daily. A proprietary preparation is 'elityran' (Bayer) which contains 0.09 mg. of thyroxine, partly synthetic and partly as thyroid extract. Two tablets are approximately equal to 3 grains (0.2 g.) of thyroid B.P.

Thyroxine.—There is no official pharmacopœial preparation. The synthetic substance contains 65 per cent. of iodine. It is available as 'eltroxin' (Glaxo) in the form of *l*-thyroxine sodium. The dose is 0.05 to 0.1 mg., which is equivalent to approximately ½ to 1 grain (30 to 60 mg.) of thyroid. Thyroxine has certain advantages over thyroid. It is a standard substance of constant composition and potency in any country. It does not deteriorate on keeping and has been shown to have as satisfactory therapeutic properties as thyroid (Hart and Maclagan, 1950).

Triiodothyronine.—There is no pharmacopœial preparation. It is available as tablets of 'tertroxin' (Glaxo) or 'cynomel' (Smith, Kline & French). The dose is 5 to 25 micrograms. Its actions are the same as those of thyroid and thyroxine, but more rapid and transient. A rise in the basal metabolic rate is produced in a few hours as compared with several days for thyroid or thyroxine. It has been found to be therapeutically effective in the initial treatment of myxœdema (Gross *et al.*, 1952), and is likely to have its main use in cases of myxœdema coma in which rapid action is desirable. But the very speed of action is in itself a danger because of the risk of inducing heart failure.

The comparative retail costs of the preparations mentioned are:—

Preparation	Dose	Cost
Thyroid. B.P.	½ grain (30 mg.)	1*s.* 3*d.* per 100 tablets
'Eltroxin'	0.05 mg.	2*s.* 9*d.* ,, ,, ,,
'Elityran'	0.09 mg.	9*s.* 0*d.* ,, ,, ,,
'Tertroxin'	5.0 mcg.	5*s.* 4*d.* ,, ,, ,,
'Cynomel'	5.0 mcg.	7*s.* 11*d.* ,, ,, ,,

INDICATIONS FOR THYROID HORMONE THERAPY

It should be axiomatic that thyroid therapy is replacement therapy and that the indication for it is hypothyroidism. If clinical evidence is not conclusive,

the diagnosis should first be established by the various tests for thyroid function before treatment is started. Apart from hypothyroidism in its various forms, there are a few conditions in which thyroid therapy may justifiably be used in order to reduce or suppress the pituitary output of T.S.H. These include cases of thyrotoxicosis with hyperexophthalmos or exophthalmic ophthalmoplegia and some cases of simple goitre. Thyroid therapy is also given, without any sound justification, in male infertility, primary amenorrhœa with or without obesity, and in obesity itself. Triiodothyronine has recently been used for the treatment of a newly described syndrome of 'non-myxœdematous hypometabolism'.

HYPOTHYROIDISM

Cretinism.—The sooner cretinism is diagnosed and thyroid therapy started the better is the outlook for normal physical development. But mental development is less predictable for it is now recognized that in some cases the mental defect is congenital and not the result of cretinism so that it does not respond to thyroid. Treatment consists in the lifelong administration of thyroid, but the initial dose must be carefully controlled as infants are very sensitive to it. One-eighth of a grain (8 mg.) of thyroid daily, or one-quarter of a grain (16 mg.) on alternate days, should be given for the first week, increasing cautiously by the same amount at weekly intervals until the optimum dose is reached. Clinically, the state of the infant's bowels is as good a guide as any. Continuing constipation indicates the need for more thyroid, and diarrhœa or looseness for less. It may well be necessary to check the dose by estimations of the serum cholesterol (normal, 150 to 220 mg. per 100 ml.) which is raised while hypothyroidism persists. Schlesinger and Fisher (1951), however, emphasize that serial measurements of the height and x-rays of the wrist are also desirable in order to guard against overdosage with thyroid. This is because thyroid therapy, while stimulating growth, also encourages closure of the epiphyses. If too much thyroid is given for too long the epiphyses will close prematurely and so bring growth to a standstill.

As the child gets older it will be necessary to increase the dose of thyroid and progress should be checked at six-monthly intervals. Once a satisfactory dose has been established for the time being, a change can be made to thyroxine in equivalent dosage if desired but, apart from the advantages already mentioned, there are no special indications.

Juvenile myxœdema.—Here the situation is rather simpler than in cretinism because the child will have passed normally through the early years of life and the mental status will be apparent. Investigations are also easier because the child may well be old enough to cooperate in basal metabolism estimations or radioiodine uptake tests. Treatment will be on the same lines as for cretinism and with the same precautions. Thus, for a child of, say, ten years the initial dose will be one-quarter of a grain (16 mg.) of thyroid, or 0.025 mg. of thyroxine, daily for a week with weekly incre-

ments of that amount up to the maintenance dose.

Adult myxœdema.—For present purposes this includes primary myxœdema and secondary myxœdema resulting from Simmonds's disease (panhypopituitarism) or from Hashimoto's thyroiditis (lymphadenoid goitre). The treatment is by thyroid or thyroxine, and the full daily replacement amount is usually about 3 grains (0.2 g.) of thyroid, or 0.3 mg. of thyroxine, in divided doses. It is particularly important not to give too much of either in the early stages for fear of inducing heart failure or anginal pain from sudden and undue raising of the heart rate. Initial doses should be half a grain (30 mg.) of thyroid, or 0.05 mg. of thyroxine, once daily for the first week, twice daily for the second week, three times daily for the next two weeks and then four times daily. The case should then be reviewed before proceeding to daily doses above 2 grains (0.12 g.) of thyroid, or 0.2 mg. of thyroxine. Any tendency to palpitations, nervousness or looseness of the bowels is an indication to reduce the dose by half a grain (30 mg.) of thyroid, or the equivalent of thyroxine, daily until the symptoms disappear.

Myxœdema coma.—In this dangerous state the therapeutic problem is one of urgency. The patient is comatose or nearly so, hypothermic, and the bodily processes are at such a low tempo that life is only just sustained. The administration of thyroid by mouth or of thyroxine by injection takes at least a week to show any manifest action because of the extremely sluggish circulation and minimal metabolic activity. Thus triiodothyronine is indicated because of its rapid action and gives ground for hope of a better prognosis than hitherto for myxœdema coma.

The condition is uncommon and few reports of the use of triiodothyronine have yet appeared in this country. But it seems reasonable to suggest 20 micrograms by intramuscular injection six-hourly until consciousness is regained, when the frequency may be reduced. But it must be remembered that in changing over to thyroid or thyroxine there will be a time lag of several days before their action is apparent. It will therefore be necessary to keep on with triiodothyronine after the patient is able to swallow tablets, but to be prepared to stop it promptly when the effect of the oral hormone commences. A close watch must be kept upon the pulse rate and body temperature—both of which will rise as improvement takes place—and any signs of tachycardia or cardiac embarrassment will call for reduction in the dose of hormone.

THYROTOXICOSIS WITH HYPEREXOPHTHALMOS OR EXOPHTHALMIC OPHTHALMOPLEGIA

In some cases of thyrotoxicosis there is a greater degree of exophthalmos than would be expected from the severity of the toxicity. This may exist before any treatment or develop afterwards with or without ophthalmoplegia. It has been assumed, but never conclusively proved, that exophthalmos is caused by an excessive output of pituitary T.S.H. or some other more specific exophthalmos-producing pituitary hormone. In view of this,

some authorities combine anti-thyroid drug therapy with thyroxine in the hope that the latter will replace the normal thyroid output and so suppress or reduce the secretion of pituitary T.S.H. Russell Fraser and Wilkinson (1953) recommended the addition of 0.1 mg. of thyroxine to 50 mg. of methylthiouracil thrice daily. Similarly, after thyroidectomy in exophthalmic patients the administration of thyroid or thyroxine is started immediately by some surgeons in order to forestall any possible hypothyroidism, which might make the exophthalmos worse by stimulating T.S.H. output.

SIMPLE GOITRE

It is generally conceded that a simple goitre is ultimately due to iodine deficiency. This may be brought about by absolute dietary deficiency, by relative deficiency when bodily demands exceed the supply, or by a variety of possible goitrogenic factors, which interfere with the proper utilization of iodine by the thyroid. As Spence (1952) pointed out, iodine deficiency leads to a diminished output of thyroxine and this stimulates T.S.H. output with resulting hyperplasia and enlargement of the thyroid. Some authorities therefore give thyroid in order to supply the deficit and so reduce T.S.H. output and the size of the goitre. This treatment is quite safe with a smooth simple goitre such as a recent puberty goitre in a girl. But it is not so safe in a simple goitre which has been present for some years and in which, as is almost inevitable, nodular change has taken place. This is because some nodules, especially the apparently solitary ones, are not above suspicion of malignancy and others may be degenerate and not amenable to reduction in size by thyroid therapy. On the whole, simple nodular goitres are better removed surgically if any treatment is indicated. The simple smooth goitres can be treated by ½ to 1 grain (30 to 60 mg.) of thyroid or the equivalent of thyroxine daily, but it is better not to exceed this dose as there is a risk of inducing thyrotoxicosis.

MALE INFERTILITY

In the past, thyroid therapy has been recommended for male infertility: that is to say, for improving the quality of a substandard seminal fluid. Since the only criterion of success is pregnancy in the female partner, and since there is such a multiplicity of possible factors involved in this, it is extremely difficult to assess the efficacy of thyroid or any other therapy. It is perfectly true that a man suffering from myxœdema may have poor quality seminal fluid as a result—although this is by no means certain—but he is very likely to have diminished libido or impotence and thyroid therapy will probably do more good by correcting the latter. But in a man without clinical evidence of hypothyroidism and with a normal libido it is most unlikely that thyroid therapy will improve the quality of the seminal fluid and it certainly should not be given for the sake of 'doing something'. Swyer (1956) has summarized the evidence on the subject and deplores the indiscriminate use of thyroid. Male infertility should first be properly investigated and testicular biopsy be carried out if necessary. Rational

treatment by gonadotrophins or testosterone is far more likely to be effective than thyroid.

PRIMARY AMENORRHŒA

The combination of primary amenorrhœa with obesity in girls at the expected time of puberty is not at all uncommon. The possibility of hypothyroidism is often raised, probably because of the erroneous but widespread belief that hypothyroidism causes obesity. There certainly appears to be some relationship between amenorrhœa and either gross obesity or gross wasting, but its nature is unknown. Thus, the periods sometimes start in formerly obese girls after dieting has brought their weight down to normal for their age—but even then it is impossible to say that the periods would not have appeared in any case. In anorexia nervosa amenorrhœa is a cardinal symptom which accompanies the loss of weight, and reappearance of the periods is an obligatory criterion of cure. Whatever may be the relationship between gross abnormalities of body weight and amenorrhœa, there is no evidence—apart from frank juvenile myxœdema—that the thyroid plays any part in it.

The temptation to use thyroid in girls with amenorrhœa—whether obese or not—should be resisted because it is correct treatment for neither amenorrhœa nor obesity.

OBESITY

The use of thyroid therapy in obesity is unfortunately all too common and seems to be based on several quite fallacious beliefs. The first is that hypothyroidism causes obesity: that is to say, increase of weight from excessive fat. This is incorrect because the patient with myxœdema is overweight due to bloating with fluid. When thyroid is given this is released and excreted with resulting fall in body weight—but not from loss of fat. In fact, patients with myxœdema usually lose their appetite and it sometimes happens that thyroid therapy stimulates it, so that they may put on more weight by eating than they lose by treatment.

A second fallacy arises from the fact that the basal metabolic rate is apparently lowered in cases of gross obesity. This is because the surface area of the body is so increased by the inert fatty covering that it no longer bears the average relationship to height and weight upon which tables for calculating surface area are based. The effect of this discrepancy is to vitiate the mathematical calculations upon which the basal metabolism result is founded, and a falsely low figure is obtained. A third fallacy is that thyroid therapy will stimulate the metabolism and so miraculously burn up the many pounds of fat which surround an obese individual. In practice it would be quite impossible to do this without giving for a long time a huge dose of thyroid which could never be tolerated.

In my experience, thyroid either makes no difference, even in surprisingly large doses of up to 4 or 5 grains (0.25 to 0.3 g.) daily, or it stimulates the appetite and makes matters worse. It can be categorically stated that thyroid therapy has no place in the treatment of simple obesity. The proper

treatment is dieting supplemented, if need be, by dexamphetamine which will reduce the appetite.

NON-MYXŒDEMATOUS HYPOMETABOLISM

This syndrome was reported by Kurland *et al.* (1955) from the United States. In their cases the basal metabolic rate was low, but thyroid function appeared to be normal according to radioiodine studies and serum cholesterol estimations. There was no response to thyroid extract or to thyroxine, but triiodothyronine both relieved symptoms and raised the basal metabolic rate. Similar cases have since been reported, but the underlying defect has not yet been elucidated.

The symptoms of which these patients complained included lassitude, nervous irritability, headache, vague limb pains, intolerance of cold, menstrual irregularity in women and diminished sexual activity in men. Unfortunately, these are common symptoms and may be present in a wide variety of conditions, both organic and functional. They have been widely publicized in advertising material to doctors concerning the indications for the use of triiodothyronine, and this has been the subject of leading articles in the *British Medical Journal* (September 22, 1956) and the *Lancet* (October 20, 1956). In both articles warnings were given against the indiscriminate use of triiodothyronine for patients with the above symptoms. It cannot be too strongly emphasized that triiodothyronine is an extremely potent substance which should not be given to any patient unless clearly indicated after full investigation.

CONCLUSIONS

The main object of this article has been to describe the characteristics of thyroid substances and to emphasize the legitimate indications for their use. What has been said applies to the present, but the future may well hold in store both a wider range of thyroid substances and a wider scope for their use. Already several synthetic modifications of thyroxine have been produced, such as triiodothyroacetic acid ('triac') and tetraiodothyroacetic acid ('tetrac'), which have shown selective ability to influence the basal metabolic rate or the serum cholesterol level separately. Much more research will be required before their therapeutic indications can be defined, but they are mentioned to show that the future of thyroid therapy is likely to be as exciting as its past.

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DEOXYCORTONE ACETATE

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DEOXYCORTONE acetate was first synthesized in 1937 by Steiger and Reichstein, and at once made a considerable impact on the management of patients with Addison's disease and, to a lesser extent, on those with hypopituitarism. It is a synthetic product, and in this, as well as in some qualitative properties, differs from the naturally occurring adrenal cortical steroid (aldosterone) with which it shares, albeit 25 times less powerfully, an effect on mineral metabolism. It was originally known as desoxycorticosterone or deoxycorticosterone, but these names have been shortened to deoxycortone.

The action of deoxycortone is that of a mineralocorticoid, which is to say that it affects electrolyte metabolism and has no action on carbohydrate metabolism, as have so-called glucocorticoids, such as cortisone and hydrocortisone. Its action is through the renal tubules and leads to the reabsorption of sodium and chloride and thus to the retention of fluid, and, also through its action on the renal tubules, to the excretion of potassium. The result is therefore a rise in the serum sodium and a fall in the potassium. If deoxycortone is given in excessive dosage, or with too much salt, œdema and hypertension will result and may be of considerable degree. Hypokalæmia from overdosage may also occur and lead to severe muscular weakness.

THERAPEUTIC ACTION

Deoxycortone has been tried as a therapeutic measure in a large number of conditions, and there are, amongst others, references to its use in epilepsy and myotonia, in rheumatoid arthritis, gout and rheumatic fever, in certain dermatological conditions, notably in psoriasis, and as an adjuvant to treatment of carcinoma of the cervix with radium. It is, however, only in the treatment of Addison's disease, in patients after adrenalectomy and, to a lesser extent, in those with hypopituitarism, that its usefulness has received general acceptance.

Deoxycortone alone, or, more usually, with the addition of capsules or enteric-coated tablets of sodium chloride, undoubtedly resulted in a very considerable improvement in the clinical state of patients with Addison's disease. These patients felt vastly better and were able to lead a normal or even arduous life. The marked hypotension which is a dominant feature of their condition was overcome and the blood pressure restored to normal. The serum electrolytes also returned from hyponatræmic and hyperkalæmic levels to normal ones. The tendencies to abnormal capillary permeability and to nitrogen retention, both of which can have serious consequences in

Addison's disease, were reversed. There was, however, no effect upon the disordered carbohydrate metabolism, with the risk of recurring hypoglycæmia, and deoxycortone alone was sometimes inadequate in preventing dangerous Addisonian crises, the control of which required, in addition, cortical extract.

All this has been changed by the advent of cortisone in the treatment of Addison's disease. Patients who had previously felt that their condition was well controlled by deoxycortone and salt expressed amazement at their new sense of well-being when given small physiological doses of cortisone acetate (37·5 to 50 mg. divided into three doses in the twenty-four hours). The abnormalities of carbohydrate metabolism were controlled and an Addisonian crisis has become largely preventable and a rare condition which, if recognized when it does occur, can be successfully treated in most instances, whereas previously it was among the gravest of medical emergencies. Even the pigmentation of the skin and mucous membranes will largely disappear after the use of cortisone, so that a well-treated patient may appear perfectly normal, whereas formerly when deoxycortone was the main method of treatment pigmentation not only persisted but was not even reduced.

Some patients with Addison's disease, or on whom bilateral adrenalectomy has been performed for the relief of deposits in bones secondary to carcinoma of the breast or prostate, are well controlled on cortisone acetate alone, with its mild action on the electrolytes. Other patients require the addition of a steroid with a more powerful mineralocorticoid action. In these circumstances deoxycortone has been, and still is, used in conjunction with cortisone, but its use is already being replaced by that of 9-α-fluorohydrocortisone (Hart, 1957; Nabarro and Walker, 1957), the approved name of which is fludrocortisone. This in its turn will probably give way to aldosterone when this becomes more readily available.

The value of deoxycortone in the treatment of adrenal insufficiency, either primary or secondary to surgical ablation or to hypopituitarism, is thus becoming diminished by the preparation of steroids with a more powerful salt-retaining action at the very time when, due to widespread surgical attack on the adrenals, it might have enjoyed a more extensive use than ever before.

METHODS OF ADMINISTRATION

Deoxycortone acetate (DOCA) can be given orally in linguettes, by intramuscular injection in oil, or as a crystalline deposit of deoxycortone trimethylacetate (D.C.T.M.A.), or by the implantation of a pellet.

Oral administration is indicated when a rapid action is required, but this can be more certainly obtained by using the intramuscular route. If a prolonged effect is the objective, subcutaneous implantation with pellets, or depot formation in muscle with crystalline deoxycortone trimethylacetate, is indicated.

'*Linguets*', containing 1 mg. of deoxycortone, have the advantage of being rapidly absorbed, but their action is weak, and absorption through the buccal mucosa can be irregular.

Intramuscular injection of *deoxycortone in oil* produces a quick and flexible effect. The dosage usually lies between 1 and 5 mg. a day, and is determined by the level of the blood pressure, and by estimations of the serum electrolytes.

The establishment of a depot of *deoxycortone trimethylacetate* in muscle allows of slow absorption, and a single injection of 30 mg. will last for approximately three weeks and be equivalent to a daily injection of 1 mg. of deoxycortone in oil.

Implantation is a relatively simple procedure and has been of much value in the treatment of Addison's disease in the past. It is, however, unsuitable for patients following adrenalectomy as their state may vary rapidly. If it is employed, 100-mg. pellets are implanted subcutaneously, the total dose being determined by the amount of deoxycortone acetate which is required by injection. Approximately 80 mg. should be given for each milligram required by intramuscular injection, and the total dosage is usually between 200 and 300 mg.

These implants will be effective for about five to six months, after which they should be removed and new ones implanted so that some accuracy in dosage can be maintained. Their waning effect will be reflected in the clinical state of the patient by a fall in the serum sodium and a rise in the potassium, together with a fall in the blood pressure. It is important to estimate the serum electrolytes even though the blood pressure is at a satisfactory level, as they may fall, indicating approaching hypocorticism, before the blood pressure or clinical state is altered. These effects can at first be controlled by the addition of increasing amounts of sodium chloride. The average maintenance dose in patients with a fully active implant is 5 g. daily, but this can be increased to 15 or 20 g. a day as the potency of the implant reduces.

CONCLUSION

Deoxycortone has been a valuable preparation in the control of adrenal insufficiency states for two decades, but it is now being replaced by recently discovered and more powerful salt-retaining steroid hormones.

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INSULIN

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It is now close on thirty-five years since insulin was first introduced to general use in the treatment of diabetes mellitus. The discovery of this hormone by Banting and Best has completely changed the outlook for the diabetic patient, and radically altered the clinical picture of his disease. As the years have passed, new aspects of the diabetic life and diabetic pathology have appeared: the tendency to arteriosclerosis, to neurovascular degeneration, and the appearance of new syndromes such as Kimmelsteil-Wilson nephrosclerosis. These degenerative changes are counterbalanced by the possibility of operating with success on the diabetic patient for surgical conditions associated with his disease or for others that may be incidental, by the successful management of pregnancy in the diabetic mother, and by the multiple years of useful life and manifold skills now achieved by the diabetic population.

There is still some degree of doubt on the part of many physicians regarding the choice of type of insulin, suitable dosage and times of injection. There is also still present a tendency to fear the consequences of an overdosage of insulin, and difficulty in differentiating such effects from other diabetic emergencies. A working knowledge of the physiology of insulin activity, with the timing of its maximum effect, is essential for the intelligent control of the diabetic patient receiving insulin.

SOURCE AND COMPOSITION OF INSULIN

Insulin is the extract of the islet tissue of the pancreas. So far, all supplies of the hormone are obtained from animal tissue. The substance was first prepared in pure crystalline form in Abel's laboratory at the Johns Hopkins Hospital in 1930. Its complete structure has been determined only recently by analysis. Although known to be a protein, its constituent amino-acids were not identified until their separation was assisted by chromatography. Its molecular weight is about 6000 and some sixteen or seventeen amino-acids enter into its composition, including glutamic acid, leucine, valine, glycine, tyrosine, alanine, aspartic acid, cystine, phenylalanine, serine, histidine, arginine, isoleucine, lysine, proline and threonine. The work of Sanger and his collaborators in Cambridge (1955) has shown that the insulin molecule consists of polypeptide chains of precise amino-acid sequence, joined at two places by disulphide linkages. Since the crystalline structure of insulin is now known, and also the nature and arrangement of its component amino-acids, it is possible that within a few years synthetic crystalline insulin will become available.

The manufacture of insulin is under licence from the Ministry of Health

according to the provisions of the Therapeutic Substances Act. Standards of potency are controlled by the Standards Laboratory of the Medical Research Council. It is essential that the potency of insulin preparations should be unified, otherwise adequate dosage for control of a new case of diabetes would be difficult and stabilization would be equally uncertain.

The unit of insulin was defined as that required to produce hypoglycæmia in the rabbit under standard conditions. The present unit is the hypoglycæmic activity of 0.0455 mg. of the international standard preparation of insulin. In all preparations of insulin for clinical use the strength in units per ml. is 20, 40, or 80, often referred to as single, double, or quadruple strength.

THE ACTION OF INSULIN

Like the internal action of other hormones, the action of endogenous insulin in the healthy individual is elusive to investigation. It is by analogy of the effects of injected insulin in the healthy or insulin-deficient body that the action of insulin in the intact person can be deduced. This analogy does not in any way elucidate the controlled formation of insulin by the healthy pancreas in response to the ingestion of mixed meals and their metabolic disposal. If we knew more about the normal stimuli to the formation and secretion of insulin and the relation of these processes to the antagonistic hormones, we should probably know more about the pathogenesis of diabetes itself.

From observations on the effect of injected doses of insulin, the hormone produces the following direct results:—

(a) Reduction in the glucose content of the blood and other body fluids.
(b) Storage of glucose as glycogen in the liver and muscles.
(c) Oxidation of glucose in peripheral tissues including muscle.
(d) Increase in the respiratory quotient towards unity.
(e) Increase of calorie production.

Associated with these are indirect results:—

(a) More complete oxidation of fats and diminished utilization of fat.
(b) More complete oxidation of amino-acids and diminished utilization of proteins.

In the healthy individual, an injection of insulin reduces the blood sugar to subnormal levels. Some individuals are hypersensitive to standard doses of insulin, and may exhibit an exaggerated hypoglycæmic response with clinical manifestations of hypoglycæmia. The fall in the blood sugar initiates a rebound produced by stimulus to insulin antagonists: pituitrin, adrenaline, thyroxine. This response may be absent, diminished or exaggerated.

The effect of adequate insulin dosage in the acute diabetic subject is much more dramatic and much more significant. The magnitude of the changes produced is greatly increased, since a set of pathological conditions is already in being at the time of impact. The blood sugar is high, there is lipæmia and acidosis; ketonæmia is present and ketones occur in the breath and urine; there is dehydration, diminished plasma alkaline reserve and, possibly, hypochloræmia. Clinically, there is a dry, red tongue, flushed face, intense thirst and polyuria, with severe glycosuria.

Adequate insulin produces immediately a fall in the blood sugar and increased oxidation of glucose by the tissues. The degree of acidosis is diminished, fat mobilization stops, lipæmia is reduced. If fluids are given, dehydration is also overcome and polyuria controlled. Clinically, the face

Insulin	Year	Introduced by	Character	Rate of activity
Soluble	1922	Banting and Best	Acid. Solution	Rapid: 3 hours
Protamine	1934	Hagedorn		Not now in use
Protamine zinc	1936	Hagedorn	Neutral. Amorphous suspension	Slow: 24 hours
Globin	1940	Reiner, Searle and Lang	Acid. Solution	Slow: 8 hours
Iso-insulin	1944	Möller	Modified insulin	Slow: 16 hours
Di-insulin	1945	Möller	Modified insulin plus soluble crystalline	Slow: 20 hours
Isophane N.P.H.	1945		Neutral suspension	Slow: 16 hours
Polyvinyl	1945	Durel and Dubost	Acid. Solution	Slow: 16 hours
I.Z.S. (lente)	1953	Möller	Neutral 30% amorphous 70% crystalline suspension	4 hours Slow: 9 hours
I.Z.S. (semi-lente)	1953	Möller	Neutral. Amorphous suspension	Slow: 4 hours
I.Z.S. (ultra-lente)	1953	Möller	Neutral. Crystalline suspension	Slow: 9 hours

TABLE I.—Preparations of insulin, arranged in chronological order.

All types contain 0.2 to 0.3 mg. of zinc per 100 units of insulin except soluble insulin, iso-insulin and isophane insulin, which contain zinc only in traces. Protamine zinc insulin contains up to 1.5 mg. of protamine per 100 units of insulin, whilst 0.4 mg. is present in the isophane type.

and tissues fill out with fluid, the thirst disappears and ketonuria is controlled. Such is the acute response to insulin. The long-term effect of repeated daily injection of insulin is more complicated still in that carbohydrate utilization returns to normal and, secondarily, protein metabolism becomes again anabolic and fat depots can be restored.

THE TYPES OF INSULIN

Numerous types of insulin (table I) have appeared on the market from time to time in this country, in the United States, in Denmark, France and Germany. The general aim has been to modify the insulin in its physical characters or rate of absorption from the site of injection, so as to simulate as far as possible the activity of normal endogenous insulin. This has not yet been achieved, but some of the newer types of insulin approach this ideal in suitable cases.

Soluble insulin has stood the test of time and is still the most potent type of insulin in severe diabetes or in acute diabetic emergencies with ketosis. The response to an injection as shown by fall of the blood sugar is rapid and diminution in ketosis is quickly observed. In a known diabetic subject in pre-coma—drowsy, flushed, dehydrated, and with Kussmaul's respiration, with acetone in the breath, a positive Rothera's test for acetone in the

urine, blood sugar of 480 mg. per cent., plasma CO_2 of 25 vol. per cent. —vigorous administration of soluble insulin is essential, in dosage of, say, 40 units at four-hourly intervals with a total dosage of 150 to 200 units in the first eighteen to twenty-four hours. In cases of actual diabetic coma, which, fortunately, are now becoming rare, larger doses may have to be given and the first dose may be given intravenously.

Iso-insulin, di-insulin, and polyvinyl insulin.—These types were investigated by Lyall and Auld (1950), who did not find any major advantage in their use after adequate clinical trial.

Globin insulin, if given in the morning, usually produces its greatest effect on the blood sugar about 4 or 5 p.m. and at this time hypoglycæmia could occur if the dose were too large.

Protamine zinc insulin does not exert its full effect until twenty-four hours after the injection. The lowest value of the blood sugar for the day is thus before breakfast. The time at which hypoglycæmia can occur is in the fasting state on waking.

Lente insulin, or insulin zinc suspension (I.Z.S.), is a mixture of amorphous insulin (30 per cent.) and crystalline insulin (70 per cent.). There are two peaks of activity. The amorphous component has its maximum effect about 11 a.m. to 12 noon, whilst the crystalline component acts most powerfully about 5 to 7 p.m. There is less definitive certainty about the times of the greatest fall in the blood sugar and they vary in different individuals. No type of insulin has so far shown such good results in suitable cases, maintaining long periods of normoglycæmia without precipitating hypoglycæmia, which is an important advantage. Varied proportions of the semi-lente (amorphous) and the ultra-lente (crystalline) types could be used, but up to date, unusual proportions of these components have tended to lead to some confusion, especially if the patient should come under the care of another physician.

Oakley (1953) reported favourable results in the control of new cases of diabetes with lente insulin. Murray and Wilson (1953) changed 28 cases of diabetes from soluble + P.Z.I. or other insulins to lente insulin. They showed improved control in 14, and equally good control in seven. In two cases control was less effective. They looked upon lente as equivalent to a mixture of soluble + P.Z.I. Of 19 cases investigated by Nabarro and Stowers (1953), 10 were unsatisfactorily controlled on I.Z.S. when the dose of insulin exceeded 48 units. Stowers and Nabarro (1955) investigated 195 patients on I.Z.S. after transfer from other types of insulin, in dosage mostly under 60 units daily. Usually an increase of insulin between 3 and 38 per cent. was required, but these workers concluded that about 90 per cent. of diabetics could be stabilized on I.Z.S. An intercurrent infection, however, caused a disproportionate degree of disturbance in diabetic control. Lawrence *et al.*, (1955) found that of 479 diabetic patients treated with I.Z.S., failure to achieve good control was met with in less than 7 per cent. of cases, whilst in over 30 per cent. of both adults and children better control was achieved than with other types of insulin. They also emphasized the difficulty found in combating infection and showed that there was a class of severe diabetics who always required partial treatment with soluble insulin.

Lente insulin was reviewed favourably by Murray in 1955. He did not suggest any maximum dose of this type of insulin which can be used with

advantage. In our own experience, if insulin requirement is much above 50 units daily, I.Z.S. may not be satisfactory and the patient is better treated with injections of soluble insulin twice daily. From experience in most diabetic clinics, it is probable that within a few years the types of insulin in most general use will be reduced to soluble insulin, protamine zinc insulin, and insulin zinc suspension lente.

DECISION AS TO NECESSITY FOR INSULIN

It is not essential to use insulin in all cases of diabetes. In the milder degree of diabetes in the late decades, particularly in the obese patient, it is often possible to treat the condition with success by dietetic restriction alone. Even when the initial values of the blood sugar are high, this may be due to excessive intake of sweet drinks taken to allay the thirst. When this phase is treated by a short period of relative starvation and deprivation of concentrated carbohydrates and sugars, the diabetic state may become much less severe than was at first supposed. If ketosis remains absent on a restricted diet, a preliminary period of treatment for some months on a reduced diet alone is beneficial and results in reduction of weight. Early treatment with insulin usually militates against weight reduction. If a sugar-tolerance test shows blood-sugar figures below 280 mg. per cent. in patients of this type, a trial on treatment without insulin is advisable.

If glycosuria cannot be controlled on restricted diet, if the blood sugar is over 300 mg. per cent. by a sugar tolerance test, and particularly if intractable pruritus is present in the female patient, it becomes essential to use insulin. Here the choice of insulin is easy: protamine zinc, starting with a daily dosage of, say, 20 units before breakfast. If this is enough, the pre-breakfast sample of urine will be free of sugar about the third or fourth morning of treatment. This indicates that the fasting blood sugar is approaching normal level. If this does not occur, the dosage of insulin can then be raised—to, say, 30 units. During this preliminary period of trial, each sample of urine passed should be tested for sugar and a record kept. In certain instances it might be advisable to use insulin even if control were possible without its use. When surgical operation is intended, e.g. for cataract, prostatic enlargement, sepsis, gall-stones, or gynæcological conditions, to facilitate healing it is advisable to achieve optimum control of the diabetic state.

THE CHOICE OF TYPE

The factors which decide the type of insulin to choose in the treatment of any case of diabetes include the following:—

(a) Rate of activity of insulin.
(b) Age of patient.
(c) Severity of diabetes.
(d) Presence of ketosis.
(e) Presence of infection or other complications.
(f) Type of diet.

Activity of insulin.—As shown in table I, the rate of activity of the various types of insulin varies considerably from the quick-acting soluble insulin to the slowest protamine zinc insulin. Thus, soluble insulin has to be given twice daily or occasionally more often. Protamine zinc insulin, globin

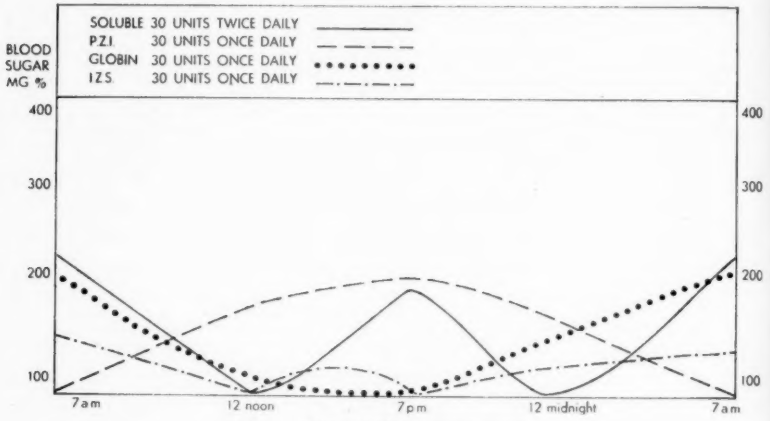

FIG. 1.—Diurnal blood-sugar curves.

insulin and lente insulin, can be given in one daily morning injection. With soluble insulin (fig. 1) the maximum effect on the blood sugar occurs about 11 a.m. and 10 p.m. Thus, the lowest value of the blood sugar in a patient well controlled on two daily injections of soluble insulin, occurs before lunch and about bed-time. It is at these times that hypoglycæmic symptoms may be expected if the blood sugar falls too low—say, below 50 mg. per cent. The highest value of the blood sugar for the day is usually the fasting value: before insulin and breakfast. The two blood-sugar values, fasting and 11 a.m., will indicate the diurnal limits of the blood sugar.

Age of patient.—Diabetes is usually most severe in the younger decades, and soluble insulin is the type of choice for use here—certainly in the initial stages of treatment. It is sometimes possible to change to a slow-acting type of insulin after stabilization is effected. If effective control has been achieved with, say, 25 units of soluble insulin twice daily, one dose of I.Z.S. may be given instead, and gradually increased if necessary. In some instances, especially in children, attempts to change to I.Z.S. are disappointing. Ketosis may appear and it is imperative to revert to soluble insulin. In the middle decades, it may be possible to start treatment with I.Z.S. if the diabetic state is not too severe and ketosis is absent. If ketosis is present, soluble insulin should be used at first and a change made to I.Z.S. after seven to ten days. In the later decades, when the diabetic state is relatively mild, protamine zinc insulin is the type of choice.

The *severity of the diabetic state*, the *presence of ketosis* and the *presence of infection* can be considered together. If the blood sugar is high, acidosis

is severe, and if infection is present, quick-acting soluble insulin is essential in dosage adequate to combat ketosis. It often happens that diabetic patients already under treatment with the protamine zinc type or zinc suspension, develop an infection and ketosis. It may be necessary to change at once to larger amounts of soluble insulin. In some cases it is sufficient to give an addendum of soluble insulin, either with the usual type or at another time of the day: say, in the evening. When the emergency is past, this addendum of soluble insulin can be withdrawn and the patient proceeds as formerly.

The type of diet chosen depends upon the weight of the patient, the appetite and the digestive capacity. In general, the overweight patient should have his weight reduced: a period of less strict diabetic control on a modicum of insulin sufficient to prevent ketosis and on a reduced diet will bring about this result. When the patient is underweight, it is best to give sufficient insulin, preferably of the soluble type, and adequate calorie intake so as to bring the body weight up nearly to normal standard.

TAKING OVER A DIABETIC PATIENT

It is often necessary to undertake the future care of a patient who has been previously under treatment with insulin. In addition to a full history and clinical examination, urine tests and blood-sugar estimations should be done and the diet should be defined. It is also advisable to see the insulin in use, and to ask the patient to indicate the dose on his syringe. Only in this way can possible confusion be avoided in describing the various strengths of insulin. Only in this way is it possible to be certain of the dosage and type of insulin and to be in possession of the data on which to make any necessary alteration.

ADMINISTRATION OF INSULIN

The best sites for injection are the deltoid region, the outer side of the thigh, the subscapular area and the lower abdominal wall. The latter site is often preferred, as it is within easy reach of both hands. If the eyesight is defective, the dose can be measured previously by a friend, or a collar can be fitted in the piston which prevents an overdose but does not ensure the full amount. In elderly patients with poor eyesight or disability of the hands, e.g. in hemiplegia, the insulin has to be given by a relative or a district nurse. Some patients, although handicapped, can give their own insulin by using the insulin gun (Palmer injector), which has the added advantage of a practically painless injection.

The times of injection should be kept uniform so far as possible; if two daily injections are given, they should be nearly twelve hours apart: say, 7.30 a.m. and 6.30 p.m., half an hour before meals.

INJECTION OF MULTIPLE TYPES OF INSULIN

Combined injections—say, of protamine zinc insulin plus soluble insulin, or soluble insulin plus globin insulin—will probably become less frequent. Hitherto, the dual use of a quick-acting insulin plus a slow-acting type has

ensured a rapid fall of the blood sugar, followed by a more gradual control throughout the 24-hour period. In some patients on two doses of soluble insulin, and when a rapid rise in the blood sugar occurred towards morning, the addition of globin insulin with the evening injection has been found to be effective. Soluble insulin cannot be combined with the lente types but the others are miscible although the soluble portion may be delayed in the process.

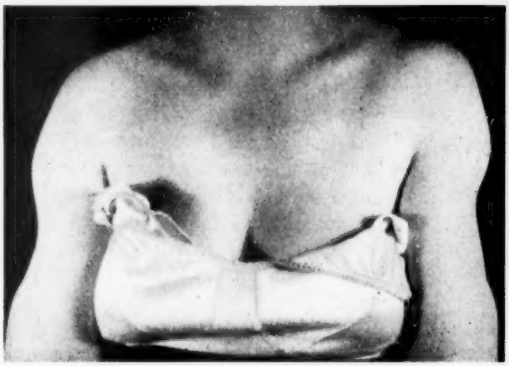

FIG. 2.—Insulin atrophy of deltoids.

UNTOWARD EFFECTS OF INSULIN INJECTION

Local effects.—Allergic reactions may occur at the site of injection. These are seldom seen with soluble insulin but are not infrequent with the other types. In most instances, the local reaction subsides after about five days. If subcutaneous œdema and superficial redness persist, another type of insulin should be tried. It may be necessary to revert to soluble insulin and it may be possible to desensitize the skin by repeated small injections.

In about 3 to 5 per cent. of diabetic patients, atrophy of subcutaneous tissue occurs at the site of injection. Such atrophic change in the upper arms may be unsightly (fig. 2). In a few patients the disappearance of subcutaneous fat may be so widespread by punctures in multiple places that a condition simulating lipodystrophia occurs, and few sites for injection remain. In others, a fibro-lipomatous swelling appears where repeated injections have been made. The rate of absorption of insulin from this area may be delayed, whilst more rapid absorption from another area may produce hypoglycæmia.

Sepsis at sites of injection is extremely rare unless a needle is broken and remains in the tissues. If a needle travels beneath fascial layers in the thigh, a deep abscess may form requiring free incision.

Hypoglycæmia.—Mild degrees of hypoglycæmia are not uncommon in the well-controlled diabetic, when the blood-sugar level approaches normal values. Increase in activity, such as produced by digging in the garden, mowing the lawn, doing the washing, running for a bus, an extra long walk, is sufficient to produce symptoms. The milder symptoms are a cold sweat, a feeling of weakness, slight slurring of the speech. These disappear within five to ten minutes on taking barley sugar, glucose or a glucose sweet. Well-trained diabetics take the precaution of consuming 10 to 20 grammes

of extra carbohydrate before taking exercise such as golf, tennis, football.

The more severe degrees of hypoglycæmia are usually due either to an error in type or strength of insulin or to deprivation of food with or without extra muscular effort. Here the mild symptoms are followed by semi-drowsy states with mental aberration, sometimes associated with violence, which may require physical restraint. Any group of symptoms simulating alcoholism may appear and the patient may perform violent or unsocial acts. In a few instances permanent damage is produced in cerebral cortical tissues, with loss of memory. Death may occur after prolonged hypoglycæmia, even although the blood-sugar value is raised by intravenous glucose drip.

Much medico-legal importance is attached to this condition in reference to driving motor vehicles and although, for legal purposes, insulin is classed as a drug, no firm ruling has ever been made with reference to charge of vehicles. Instances of hypoglycæmia while driving are rare, and few have come to court.

RECOGNITION AND TREATMENT OF HYPOGLYCÆMIA

Symptoms of weakness, sweating, tremor, pallor, mental confusion occurring at the time of maximum insulin activity should always be treated in the first instance as hypoglycæmia by administration of sugar in any form of sweet drinks. Normal habits and behaviour return within ten minutes, usually on taking half an ounce (15 g.) of glucose. In the differential diagnosis, cerebral thrombosis, cerebral hæmorrhage, epilepsy, Ménière's syndrome, coronary thrombosis, perforation of a peptic ulcer, or the onset of diabetic coma may have to be considered. In none of these conditions can glucose do harm, with the exception perhaps of a perforation. Sugar should be given as soon as possible, while the patient can still swallow. If the swallowing reflex is lost, sugar can be given by stomach tube, a route which may be difficult and messy on account of struggling, or dangerous if sugar is inhaled. Administration by the intravenous route is better, giving 100 ml. of a 33 per cent. glucose solution. It is well to produce a mild hypoglycæmic episode in the new diabetic patient. He is thus trained to recognize the premonitory symptoms and warned when to take his emergency ration of sugar. Although most patients experience warning signs, others, especially with the slow-acting insulins and if asleep, may sink into hypoglycæmia, unknown to relatives or nursing staff.

DEEP INSULIN THERAPY

Deep insulin therapy is designed to alter the mental state, particularly to interrupt the progress of mental deterioration in schizophrenia. It consists of the induction of hypoglycæmic coma for a brief period of twenty to thirty minutes on repeated occasions. A normal course consists of 50 such comas. The dosage of insulin necessary to induce coma is discovered for each individual and varies from 40 to 300 units. The injection is given intramuscularly at 7 a.m., the patient having had no food since 8 o'clock on the previous evening.

The symptoms of hypoglycæmia—profuse perspiration, tremors and twitchings, restlessness, and drowsiness—progress through a stage of sopor to deep coma. When this has continued for twenty minutes the patient is roused by the introduction of half a pint (280 ml.) of tea in which is dissolved 6 oz. (185 g.) of sugar, into the stomach by nasal tube. It is an important part of the technique to wash out the stomach first and aspirate any bile-stained mucus, which often collects and would hinder absorption. In a favourable case, consciousness returns rapidly and ten minutes after the introduction of the sugar into the stomach the patient is able to sit up and take a light meal of cornflakes, sugar and milk. If the return of consciousness is slow, an injection of 8 to 10 minims (0.5 to 0.6 ml.) of solution of adrenaline hydrochloride B.P. is often helpful. Sometimes recovery is delayed, and an intravenous injection of 100 ml. of 33 per cent. glucose is given. This is rapidly effective in restoring consciousness.

Certain patients have a tendency to undergo hypoglycæmic convulsions. These are considered unfavourable and, should such an event occur, the treatment is abandoned for that day, the hypoglycæmic state being terminated by giving a sugar drink as soon as consciousness returns after the fit. Thereafter, the patient is given 2 grains (0.12 g.) of phenobarbitone daily, and the treatment continued.

There is a tendency by many psychiatrists to abandon insulin therapy in favour of less expensive and more rapid techniques such as electrical stimulation therapy. We have, however, ample clinical experience of cases in which such rapid techniques have often failed or have only been temporarily successful, and insulin given subsequently has stabilized the mental state. Generally, improvement becomes manifest after 20 comas, and is progressive until the end of the treatment. The treatment occupies the patient's forenoons and in the afternoon he pursues the ordinary programme of occupational and recreational therapy.

A late shock occasionally occurs and patients are warned to carry a few cubes of sugar to be taken if they begin to perspire.

ORAL HYPOGLYCÆMIC AGENTS

No consideration has been given to insulin substitutes, e.g. 'synthalin', carbutamide and tolbutamide, which can be given orally for the treatment of some milder types of diabetes. These substances do not simulate the physiological actions of insulin and may produce untoward side-effects.

I am indebted to Dr. A. M. Wyllie for the paragraph on deep insulin therapy.

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POSTERIOR PITUITARY EXTRACTS

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THE pituitary or hypophysis has long been acclaimed as the master—or even the dictator—gland, or as 'leader of the endocrine orchestra'. Its functions are widely spread throughout the body, and it particularly influences the formation and liberation of other hormones. On the other hand, its activities in turn are modified in accordance with the concentration of these other hormones, and, like the suprarenal medulla, but unlike most endocrines, it is probably under some degree of nervous control. The literature on such nervous control is extensive: there are, for instance, 450 references in G. W. Harris's 'Neural Control of the Pituitary Gland' (1948).

For therapeutic purposes pituitary secretions may be considered as arising from the posterior or anterior lobes. The pars intermedia is rich in a principle which produces expansion of amphibian pigment cells (melanophores), but for which there is no known application in man. There is no doubt that the pituitary principles act in very low concentrations. So potent are they that detectable or even measurable concentrations from one lobe may be found as impurities in extracts from others. The slight traces of posterior lobe hormones found in the anterior lobe have been used as an argument against the formation of these compounds by the pars glandularis. It has been suggested that the hypothalamus influences the production of hormones in the pars nervosa, or alternatively (Leveque and Scharrer, 1953) that it produces the hormones which pass along nervous pathways to be stored against need in the gland. Section of the hypothalamico-hypophysial tract produces not only atrophy of the neural lobe and diabetes insipidus but degeneration in the neurones of the hypothalamic nuclei.

PRINCIPLE OR PRINCIPLES?

The demonstration by Oliver and Schafer, in 1895, of the presence in the pituitary of a vasopressor principle was quickly followed by investigations of other actions—on the uterus, gut, kidney, and mammary gland—and by attempts at the localization of these principles in different parts, and even cells, of the gland, and studies of their chemical nature. The long-burning question as to whether there was only one active principle or more in the posterior lobe was settled in 1926 by the separation of vasopressin from oxytocin by Kamm (Kamm *et al.*, 1928). The nature of these principles continued to elude the chemists. They were thought possibly to be fractions of a protein of molecular weight about 30,000 with a high sulphur content (Van Dyke, 1939, 1942), certain polypeptides carrying the active groups which affected blood vessels, uterus or kidney. It was established that both

vasopressin and oxytocin were destroyed by digestion with alkali or trypsin, but resisted pepsin and acid. In a comparative study of their fate in the body, Morgan Jones and Schlapp (1936) demonstrated that:—

(1) They disappeared from the blood after intravenous injections at the same rate, and nearly all within an hour.

(2) The active principles do not enter the red blood corpuscles, nor are they destroyed on incubation with blood, kidney or spleen.

(3) Destruction of both proceeds at the same rate on perfusion through the liver or on incubation with liver, but not with boiled liver, suggesting enzyme destruction.

(4) Up to a third of the pressor principle injected intravenously can be recovered from the urine, and this principle is not destroyed by incubation with sterile urine. (Oxytocin estimations are very uncertain in the presence of urine.) At no point in this investigation was there any evidence of any difference in the way in which the body dealt with the two principles.

The establishment of the nature of these principles by du Vigneaud, in 1953, marked an important milestone in biochemistry. He showed that

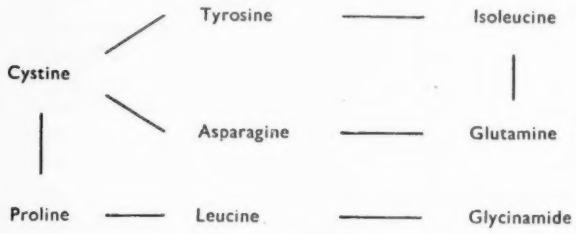

FIG. 1.—Oxytocin.

there are certain differences in the amino-acid groupings between vasopressin and oxytocin and lesser differences between samples of vasopressin, according to the species of animal whence the glands are obtained.

PREPARATIONS

Oxytocin is the first polypeptide hormone to be synthesized. It has a ring consisting of tyrosine, isoleucine, glutamic and aspartic acids as amides with a cystine residue and a side chain of proline, leucine and glycinamide (fig. 1). In vasopressin the leucine is replaced by phenylalanine, the isoleucine by lysine or arginine, according to the source of the gland (pig or cattle). The synthetic preparation gives the characteristic reactions of the natural material, and titrates at nearly 100 units/mg. (The international unit is the activity of 0.5 mg. of the international standard preparation of dried gland.)

A new method of synthesis was developed by Boissonas *et al.* in 1955, which was adapted to large-scale production, and synthetic oxytocin was made available under the name of 'syntocinon' (Sandoz). The *British Pharmacopœia* amended the official requirements of its monograph to allow of the use of this synthetic hormone as well as that extracted from the gland. The former has the advantages of unvarying potency and complete freedom

from vasopressin. It is supplied in two strengths: 'syntocinon 5' (5 units in 0.5 ml., equivalent to B.P. injection of oxytocin and used in the same way), and 'syntocinon 2' (2 units in 2 ml., which is convenient for the preparation of intravenous drip infusions, regarded as the method of choice for the induction of labour).

The *British Pharmacopœia* 1953 provides two injections of posterior lobe: injection of oxytocin (10 units/ml.), 2 to 5 units subcutaneously or intravenously; injection of vasopressin (20 units/ml.), 5 to 15 units subcutaneously or intravenously.

As would be expected from what we know of their chemistry, these preparations are useless if ingested, but for the more convenient control of diabetes insipidus a pituitary powder containing 200 units/g. (or 10 per cent. of standard powder) may be used as a snuff and the antidiuretic hormone is absorbed satisfactorily from the nasal mucosa. 'New and Non-Official Remedies' recognizes an oily injection which serves as a slow-release antidiuretic therapy.

The injection of pituitary containing both oxytocin and vasopressin was deleted from the *British Pharmacopœia* 1953, but there may be a use for it still, as there is evidence that both principles contract the uterus, but at different phases in its cycles. Although vasopressin has less effect than oxytocin on the human pregnant uterus, it has marked oxytocic effects on the non-pregnant uterus, causing increased tone and less relaxation between contractions. Some observers maintain that the human parturient uterus is equally sensitive to both principles.

UTERINE ACTION

Pituitary extract was introduced into therapeutics as a powerful stimulant of plain muscle by Blair Bell in 1919. He found it particularly effective on the uterus, and preferred it to ergot because he considered it acted more quickly and produced less spasm, although the action was less prolonged. Today, ergometrine is preferred in the treatment of post-partum hæmorrhage. The incidence of spasm with either drug is probably more dependent upon dosage than on the choice of oxytocic. With excess of either drug before delivery there are risks that contractions may be so powerful as to delay labour, asphyxiate the fœtus, produce intracranial hæmorrhage, cause premature separation of the placenta, laceration of the cervix, or even rupture of the uterus. Accordingly, many obstetricians reserve these drugs for use after the delivery of the placenta, to prevent or relieve post-partum hæmorrhage, and some use them thus as a routine.

The uterus is not always sensitive to oxytocin, but only while it is not 'protected' by progesterone or sensitized by œstrogen. It thus shows a cycle of sensitivity which was used by Knaus (1926) to fix the date of ovulation around the twelfth day in the normal 28-day cycle. The sensitivity of the uterus to oxytocin as term approaches may be increased by the administration of œstrogens.

The risks attending the administration of oxytocics before the uterus has emptied itself have been re-assessed in relation to the study of the synthetic hormone (fig. 2). Provided the dose is carefully controlled, oxytocin may be used either for the induction of labour or to stimulate inadequate uterine contractions. For induction, an intravenous infusion using 10 or 5 units per litre is preferred, although much weaker solutions are recommended by other obstetricians, and the rate of infusion is adjusted to meet individual requirements: 0.5 ml. per minute is used initially and this is adjusted to elicit and maintain a satisfactory uterine response. If given intramuscularly, injections of 0.5 to 2 units are repeated hourly until contractions are induced, and not more than half-unit doses should be used to maintain adequate contractions. The total requirements of a patient are usually less than 5 units. Because of the risk of uterine 'banding', oxytocics are not usually recommended to expedite delivery of the placenta, except perhaps in Cæsarean section.

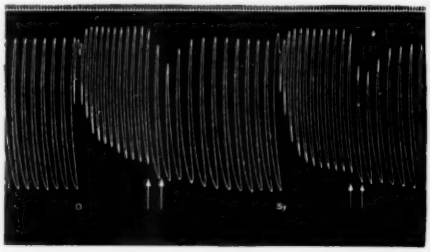

FIG. 2.—To show the similarity of the effects of natural (o) and synthetic (sy) oxytocin on an isolated slip of human uterine muscle. Time in minutes (Konzett *et al.*, 1956).

RENAL ACTION

In the anæsthetized experimental animal, vasopressin produces a swelling of the kidney which parallels the rise in blood pressure, and an increased excretion of urine while the kidney is dilated. There may also be increased urine flow because of contraction of the bladder. This diuresis, however, is soon followed by a period of reduced secretion, and may not appear if the drug be given other than intravenously, or if the dose be too small to raise the blood pressure significantly.

In the unanæsthetized animal, including man, subcutaneous or intramuscular injections are antidiuretic, and postpone the diuresis which would normally follow the ingestion of fluid. This action, believed to be the main physiological function of the posterior lobe, if not the only one, is due to increased reabsorption in the renal tubules. The release of vasopressin from the normal gland has been shown by Verney (1947) to be dependent upon the nervous control of the gland from the osmoreceptors which respond to the state of hydration of the blood. Volume-receptors have also been postulated in the cerebrum. Salt diuresis is not delayed by vasopressin, and adrenal cortical hormones antagonize the antidiuretic hormone.

The treatment of *diabetes insipidus* is largely a question of how to maintain the desired reabsorption of water in the tubules. Some patients are comfortable on two injections a day—others find they need injections every

two hours, but may be spared this by the use of oily injections of vasopressin tannate or of a pituitary snuff. Vasopressin tannate (5 pressor units in 1 ml. of oily injection) may afford relief for forty-eight hours. As might be expected, the onset of its action is slow and the ordinary injection of vasopressin may be required during the first day or two. Sometimes this has a sustained effect and need only be given once a day, but usually two or three or even more injections are required. The usual dose of pituitary snuff is 0.15 g. daily in divided doses—each dose may last for six to ten hours. As an alternative to snuff, cotton-wool soaked in the injection of vasopressin may be applied to the nostrils three or four times a day for a few minutes, but this, of course, will produce local vasoconstriction and is not usually as satisfactory as the use of snuff. Alternatively, 0.5 ml. of injection of vasopressin B.P. may be applied from a nasal spray three times a day. Unfortunately, sufferers from diabetes insipidus may lose their response to the antidiuretic hormone. It has been suggested that vasopressin should be renamed antidiuretin or ADH (antidiuretic hormone). The kidney is affected by a concentration of 1 in 3×10^{11}.

The water retention induced by the hormone can lead to the hydræmia and œdema of 'water disease' with headache, nausea and asthenia. In the epileptic the postponement of a normal water diuresis by vasopressin may precipitate a fit and this has been used in the diagnosis of doubtful cases of epilepsy. Half a pint of water (280 ml.) is given every two hours, and injection of vasopressin B.P., 1 ml. every four hours. Forty hours of this will not produce a fit, except in an epileptic.

ACTION ON CIRCULATION

In the experimental animal small doses of vasopressin raise the blood pressure, especially when this is initially low, by contraction of capillaries and arterioles. Large blood vessels are little affected. The vasoconstriction is particularly marked in the skin and splanchnic area. Larger doses may provoke cardiac irregularities because of increased peripheral resistance and coronary constriction. In the normal human subject intravenous vasopressin may result in a terrifying cutaneous vasoconstriction without appreciable rise in blood pressure or change in pulse rate, lasting for fifteen to thirty minutes. In the treatment of hæmorrhage and 'shock' the combination of vasopressin with intravenous fluids may be dramatically effective, but the lasting benefit is attributed to the fluid rather than to the pituitary, and to raise the blood pressure in shock with vasopressin without transfusion may well intensify the circulatory failure. The various sympathomimetic amines, and noradrenaline in particular, are now regarded as better and safer pressor agents, since they do not reduce coronary blood flow as vasopressin does.

ACTION ON PLAIN MUSCLE

Whilst it is easy to demonstrate stimulation of the gut and bladder in the experimental animal or on isolated preparations of plain muscle, other

viscera are not nearly as sensitive as the uterus is to pituitary principles. Vasopressin is sometimes used in paresis of the gut or bladder, or to clear accumulations of gas from the gut prior to radiography: 5 to 20 units may be required and especially affect the colon. Oxytocin inhibits isolated preparations of circular muscle from the gut which are stimulated by vasopressin, but contracts the longitudinal muscle. The vasoconstriction may reduce the efficacy on the plain muscle when used clinically, in comparison with the effect on isolated plain muscle preparations.

When posterior pituitary is injected into a lactating mammal, milk is expelled. This is not due to a lactogenic action, but to contraction of the mammary plain muscle and extrusion or 'let-down' of preformed secretion. In the cow, oxytocin appears to be liberated from the posterior lobe under the stimulus of suckling or milking of the teats and to be necessary for the 'let-down' of milk from the glands. Because of this regular liberation during lactation, there is loss of oxytocin but not of vasopressin from the gland. Such independent or differential release of one hormone is proof of the existence of two post-pituitary hormones in the body, and it may well be that the physiological function of oxytocin is on the breast just as that of vasopressin is antidiuretic.

It is a sort of rough justice that where the *Pharmacopœia* has departed from its principles and named two hormones in accordance with their main therapeutic and believed-physiological actions (in the absence, of course, at that time of precise knowledge of their chemistry) neither name should escape the later criticism of failing to indicate the real function of the hormone in the body.

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GONADOTROPHIC HORMONES

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ALTHOUGH the study of the gonadotrophic hormones is still in its infancy there is a huge literature on the subject dealing with almost every conceivable aspect in every available experimental animal, and to a lesser extent in human beings. Two books in particular deserve mention: 'Biological Actions of Sex Hormones' by H. Burrows (1949) and 'The Management of Menstrual Disorders' by C. F. Fluhmann (1956), and readers are referred to them for the detail that must of necessity be left out of a short article.

The gonadotrophins, which are of two kinds, are derived either from the pituitary or from the placenta. They are complex glycoproteins of varying molecular size which are not stored appreciably in the body but are inactivated in the bloodstream or excreted in the urine. It is thought that the carbohydrate part of the gonadotrophic molecule contains the active radical, whereas the protein part is hormonally inert. The protein fraction, which is probably specific for each species, may act as a mild antigen if injected and lead to antibody reaction. When gonadotrophins are injected over a period of time there is usually a falling off in effect and there is some uncertainty as to whether this is due to the formation of true antigonadotrophins or no more than a manifestation of the antigen-antibody reaction already mentioned.

PITUITARY GONADOTROPHINS

Three of these are described: *the follicle-stimulating or follicle-ripening hormone* (F.S.H. or F.R.H.), the *luteinizing hormone* (L.H.), and *lactogen*, which is also known as prolactin, the mammogenic hormone and luteotrophin. Neither follicle-ripening hormone nor luteinizing hormone has international standards of activity. The international unit for prolactin is that of 0.1 mg. of a standard preparation.

Follicle-ripening hormone (F.R.H. or F.S.H.), as its name implies, causes the development and ripening of the Graafian follicle and leads to the production of œstrogen; it does not cause ovulation, for which luteinizing hormone is required. The activity of F.S.H., which is slight in childhood, increases slowly throughout the years of reproductive activity until at and after the menopause it is present in excess in the urine. In the male the peak excretion in the urine is said to occur between the ages of 60 and 70. Follicle-ripening hormone and luteinizing hormone from the pituitary are not available in any quantity commercially: a number of preparations is available which combine extracts of the anterior lobe of the hypophysis, usually along with gonadotrophins derived from pregnancy urine.

It is generally agreed that, besides follicle-stimulating hormone the pituitary produces *luteinizing hormone* but, as it has not yet been possible chemically to separate these two substances, it is not absolutely certain that there are two substances. For example, gonadotrophins prepared from the urine of women after the menopause show predominantly a follicle-ripening action until the dose is increased when a luteinizing effect can be imposed. The whole subject is further complicated by the mutual influence of luteinizing hormone and follicle-ripening hormone on each other, and also by the effect of the gonadal hormones on the output of the gonadotrophic hormones: for example, in order to obtain a luteinizing-hormone response both œstrogen and follicle-ripening hormone are thought to be required.

There seems a good deal of doubt what part *lactogen* (luteotrophin) plays in human beings. Fluhmann (1956) doubts whether it is justifiably included among the gonadotrophins, pointing out that its gonad-stimulating action has been found only in the rat. Burrows (1949), however, writes: 'the maintenance of established corpora lutea in a functional condition by lactogen seems wells established'.

CHORIONIC OR PLACENTAL GONADOTROPHIC HORMONES

Two preparations are available: *equine gonadotrophin*, which is prepared from the serum of pregnant mares between the 37th and 150th day of gestation, and *chorionic gonadotrophin* prepared from the urine of pregnant women. Both these substances have anterior-pituitary-like effects but, as they are derived not from the anterior pituitary but from the placenta, differences are to be expected. In clinical practice the former preparation is judged to be follicle stimulating, the latter luteinizing in its effect.

The activity of *equine gonadotrophic hormone* is standardized in terms of the international unit, which is the activity of 0.25 mg. of a standard preparation stored at the National Institute for Medical Research, London. This hormone stimulates and causes ripening of the follicle and is inactivated within the animal's body, as none is excreted in the urine. It is not thought by itself to cause ovulation, and its biological action can be distinguished from pituitary gonadotrophins and chorionic gonadotrophins.

Chorionic or *placental gonadotrophin* is present in quantity in the urine of pregnant women, especially in the early months of pregnancy. There is a peak excretion some time between the 50th and 80th day of gestation. This is the substance responsible for the Aschheim-Zondek, Friedman, Hogben, and other biological tests for pregnancy. It is standardized in terms of the international unit, which is the activity of 0.1 mg. of a standard preparation. The effect of chorionic gonadotrophin is somewhat different from that of pituitary gonadotrophins. In pregnancy it is important because the increasing production of œstrogen and progesterone completely inhibits pituitary action, and without some other mechanism to maintain the corpus luteum the pregnancy would not continue. Placental gonadotrophin is often

thought of as identical with the luteinizing hormone of the anterior pituitary but this is probably not so, although clearly the relationship is close.

GONADOTROPHINS IN CLINICAL PRACTICE

The lack of pituitary gonadotrophic hormone in the adult female is seen in the condition of pituitary necrosis (Simmonds's disease), in which, as a result of shock and hæmorrhage, perhaps in childbirth, partial or complete necrosis of the anterior pituitary lobe occurs. Besides the effects of lack of other anterior pituitary hormones, the absence of any gonadal stimulus leads to a disappearance of many of the secondary sex characteristics of the adult woman. Some shrinkage of the breasts, loss of pubic and axillary hair, premature senile atrophy, and shrinkage of the vulva and vagina, disappearance of glycogen from vaginal cells, shrinkage of the uterus and disappearance of the endometrium and consequent amenorrhœa are the main features of this condition. Overactivity of pituitary gonadotrophic secretion is best illustrated by precocious sexual development which can on occasion occur at a remarkably early age. Little girls scarcely out of infancy have been known to conceive and carry children, having previously menstruated for some years. For example, Lina Medina had her first child when she was just over 5 years of age. Such are examples of the rare extremes of pituitary gonadotrophic activity.

Minor vagaries of function also occur, but in the human female their recognition presents so many difficulties that diagnosis is often little more than an intelligent guess, and treatment is largely empirical. These difficulties result from the lack of precise methods of assay of the gonadotrophins and the lack of clearly measurable criteria by which the gonadotrophic activity can be recognized. The effect of gonadotrophic therapy on the boy with the undescended testis (I have been told that such treatment is useless) is as difficult to judge as the effect of the same therapy on the young woman thought to be ovulating only infrequently.

GONADOTROPHIC THERAPY

In gynæcological practice the three main reasons for considering gonadotrophic therapy are amenorrhœa or hypomenorrhœa, anovular menstruation, and infertility. There are many conditions causing these faults and treatment must depend upon accurate diagnosis. Amenorrhœa, for example, may be due to such widely different lesions as imperforate hymen, congenital absence or underdevelopment of the uterus, gonadal dysgenesis and anorexia nervosa, or it may occur without there being any obvious lesion present.

On the question of the advisability or otherwise of treating amenorrhœa when there is no gross fault to be found there is a number of known facts which should be kept in mind. In the first place the anterior pituitary is under the influence of the hypothalamus, and therefore the brain as a whole.

This relationship is confused and complex and so the correction of any diminished pituitary function may necessitate a most careful study of the person as a whole: not just in regard to their physical well-being, but also taking note of their whole attitude to life and themselves. It is known that pituitary activity is sensitive to many stimuli, e.g. sight, smell, cutaneous sensation, hearing, so it may be that many fears and other psychological

Preparation	Manufacturer	Source
Chorionic Gonadotrophin B.P.		
Injection of chorionic gonadotrophin B.P. Antuitrin-S (Antroidin) Gonadotrophin L.H. Gonan Pregnyl	Official preparation Parke, Davis Paines and Byrne British Drug Houses Organon	Luteinizing hormone from pregnant women's urine
Serum Gonadotrophin B.P.		
Injection of serum gonadotrophin B.P. Gestyl Gonadyl Serogan	Official preparation Organon Roussell British Drug Houses	Follicle-stimulating hormone from pregnant mares' serum
Combined Products		
Ambinon-A	Organon	(1) Fraction of extract of anterior lobe of the hypophysis, purified to contain the thyrotrophic and gonadotrophic factors combined with (2) Chorionic gonadotrophin from pregnancy urine.
Ambinon-D	Organon	Contains 300 guinea-pig units of thyrotrophic hormone and 10 synergic rat units of gonadotrophic hormone
Synapoidin	Parke, Davis	Combination of F.S.H. of anterior lobe of the hypophysis and chorionic gonadotrophin from pregnancy urine

Table I.—Some preparations of gonadotrophic hormones and anterior pituitary hormones.

upsets can inhibit this action. Chronic underfeeding inhibits gonadotrophic function in animals. In women a similar effect has been reported by Sydenham (1946), who reported an incidence of 60 per cent. of amenorrhœa in women prisoners of war fed on a diet deficient in protein and vitamins and with only 1,600 calories per day. A deficiency of vitamin B complex adversely affects pituitary function. Deficiency of vitamin E in the male leads to testicular damage which in turn may lead to some increased production of the gonadotrophins. In the female the picture is not clear, although the balance of evidence is that vitamin E deficiency reduces the gonadotrophic potency of the anterior pituitary.

Attention to general bodily and psychological health is therefore clearly important in the management of amenorrhœa. Endocrine treatment may be

considered in two different ways: (a) administration of pituitary hormones, and (b) œstrogen-progesterone therapy aimed at causing some uterine bleeding and re-establishing normal pituitary activity. There is some justification for the latter view as it is known that in animals partial gonadectomy results in an excess production of F.S.H. Thus, it may be argued, in theory at least, that gonadal hormones during their administration will inhibit pituitary function but on withdrawal pituitary activity will return. So far as human beings are concerned, the effect of the gonadal hormones on gonadotrophic activity is uncertain.

Frank (1940) maintains that, whereas large doses of œstrogen inhibit gonadotrophic action, small doses given for short periods increase it. There is, however, a difficulty here in that the gonadal hormones can have a stimulating action on the gonads themselves. Rowlands and Sharpey-Schafer (1940) showed in human beings that œstrogens inhibited gonadotrophic function. Hisaw, Fevold, Foster, and Hellbaum (1934) believed that the effect of œstrogen is to stimulate production of luteinizing hormone while suppressing that of follicle-ripening hormone.

Androgens are similar to œstrogens in the check they impose on the anterior pituitary, and this action has also been confirmed in the human female. Progesterone also inhibits pituitary gonadotrophic activity.

It must, however, be made clear that for all the high hopes of effective endocrine therapy for amenorrhœa the results have been most disappointing. Bishop (1950) writes:—

'Perhaps the most significant observation with regard to the endocrine treatment of amenorrhœa is that in the last five years or so very few reports concerning it have appeared in the literature. It would seem that even the enthusiasts have abandoned it as a hopeless proposition. . . . Two trends have developed from this disillusionment: the first is a clearer recognition that amenorrhœa is a symptom and not a syndrome. It may result from innumerable causes and, though it may be one of many manifestations of ill health, it does not itself give rise to ill health; thus it does not require treatment *per se*'.

Besides, it must always be borne in mind that the woman who has amenorrhœa is not necessarily infertile. On a number of occasions I have been looking after a patient admitted to hospital for investigation of what was thought to be abnormal amenorrhœa only to find that a normal pregnancy had supervened.

Adolescent menorrhagia and the metrorrhagia associated with endometrial hyperplasia are two other conditions for which gonadotrophic, and particularly chorionic gonadotrophic, therapy has been tried, but mostly such treatment is now out of favour. Fluhmann on the subject of adolescent metrorrhagia, for example, writes:—

'The anterior pituitary preparations available today are of no value and in some instances appear to intensify the episodes of bleeding. Chorionic gonadotrophin long has been recommended but its employment has been abandoned by most authorities in this country. The most useful preparations are estrogen, progesterone, or combinations of the two'.

Infertility.—Just as amenorrhœa and hypomenorrhœa and metrorrhagia have many different causes so it is with infertility. In any particular case a diligent search must be made for the principal factor at work. A post-coital examination is required to exclude male factors. If aspermia or oligospermia is detected gonadotrophic therapy may be tried, but again the results are very disappointing. Indeed, in this condition if hormone therapy is to be seriously considered then testosterone should be preferred and should be given sublingually to avoid the inactivation that is thought to take place in the liver.

If tubal occlusion is found to be the cause of the infertility then clearly no hormone therapy has any place. A study of the daily temperature combined with examination of endometrium obtained at premenstrual biopsy may indicate that ovulation is infrequent, and it is in this type of case that therapy by gonadotrophic hormones must seriously be considered, and either the course of treatment recommended by Hamblen and his colleagues (1941), or that recommended by Rydberg and Pedersen-Bjergaard (1943), should be chosen. The former workers recommended ten daily injections of approximately 400 i.u. of serum gonadotrophin, followed by ten daily injections of approximately 300 i.u. of chorionic gonadotrophin. The Danish workers recommended five daily injections of 3000 units of serum gonadotrophin followed by three daily injections of 1,500 units of chorionic gonadotrophin on alternate days. In spite of all claims, however, the results of therapy are disappointing.

CONCLUSION

Treatment with the gonadotrophic hormones at present available (see table I) has proved so disappointing that they should probably not be used in general practice, unless on the advice of a consultant.

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PROGESTERONE AND ETHISTERONE

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It is now recognized that the cyclical changes which occur in the ovaries during reproductive life are mediated through the pituitary gonadotrophic hormones.

THE MENSTRUAL CYCLE

Each month, beginning at the menarche and ending at the menopause, several primordial follicles (each containing an ovum) develop in the ovaries under the stimulus of the follicle-stimulating hormone of the anterior pituitary gland. Generally, however, only one follicle reaches full maturity and ruptures on the surface of the ovary—ovulation; the others undergo atretic changes and finally merge into the stroma of the ovary. During their development, the follicles secrete œstrogen or female sex hormone. Whilst follicular growth is stimulated by the pituitary follicle-stimulating hormone, œstrogen secretion is induced by the pituitary luteinizing hormone. Ovulation occurs approximately about the middle of the menstrual cycle, that is, about fourteen days before the onset of menstruation. After the ovum has been extruded, the follicle is transformed into a corpus luteum or yellow body, the stimulus for which is the pituitary luteinizing hormone.

Until the beginning of the present century, the corpus luteum was considered to be a degenerative process in the life of the Graafian follicle. In 1903, however, Ludwig Fraenkel showed that it forms an important part of the cyclical changes in the ovary, and is a vital structure which protects the fertilized ovum. The experimental work of Fraenkel, that the corpus luteum is an organ of internal secretion, was later confirmed by numerous investigators. The specific hormone of the corpus luteum was not identified, however, until 1929, when Corner and Allen succeeded in extracting the hormone from the corpus luteum, and devised an assay method for corpus luteum extracts. The hormone was isolated in crystalline form and its chemical structure determined in 1934 by several groups of workers, and by common consent was termed progesterone.

Progesterone is metabolized in the body, particularly in the liver, and is excreted in the urine as several reduction products, the most important of which is pregnanediol. This is an inert substance, without biological activity. A sensitive chromatographic method for the assay of urinary pregnanediol has recently been elaborated (Klopper *et al.*, 1955).

The amount of pregnanediol excreted in the urine represents about ten to twenty per cent. of the endogenous progesterone secretion.

It was thought initially that the corpus luteum was the only source of progesterone secretion. It is now known that the adrenal cortex is also

implicated. This adrenal secretion accounts for the pregnanediol excreted during the first half of the menstrual cycle, and certainly for the considerable amounts which are sometimes present in cases of adreno-genital syndrome. Furthermore, pregnanediol increases in concentration during pregnancy, and falls sharply after parturition. The rise in concentration of pregnanediol occurs even when the ovaries have been removed early in pregnancy, thus indicating the placenta as a source of progesterone production.

ACTION OF PROGESTERONE

Progesterone is primarily a progestational hormone, necessary in animals at least for the maintenance of pregnancy. It is a steroid with the same basic chemical structure as androgen and œstrogen. Progesterone has little effect on tissues and organs which have not been previously or simultaneously sensitized or primed by œstrogen. Its important physiological actions are:—

(1) It converts the proliferative phase of the uterine endometrium into the premenstrual or secretory phase, and thus prepares a suitable environment for the embedding of the fertilized ovum, should conception occur. Coincident with implantation of the ovum, progesterone induces the decidual reaction in the endometrial stroma. The small connective-tissue cells of the stroma are transformed into large, oval, epithelioid cells, which act as a protective mechanism against the invading trophoblast.

(2) It promotes hypertrophy of the myometrium, and has a definite effect on uterine contractility. During the first half of the cycle, the uterine contractions are characterized by being frequent, of high tonus and low amplitude, whereas during the secretory or second half of the cycle, the contractions are much slower, have an increased amplitude, but have considerably lowered tonus. In this way, progesterone promotes a favourable environment for the implantation of the ovum.

(3) It stimulates the development of the alveolar system of the breast.

(4) It raises the basal temperature by a few fractions of a degree, so that the temperature during a normal ovulatory cycle is biphasic.

(5) Like the other sex steroids, progesterone induces sodium and fluid retention.

(6) It relaxes the smooth muscles generally—in the blood vessels, ureters and alimentary tract. This probably accounts for the occurrence of varicosity of veins, hydro-ureter and constipation, which are common during pregnancy.

Progesterone can be extracted from natural sources, such as hogs' ovaries, or synthesized from cholesterol or stigmasterol (a plant sterol found in the soya bean). It is administered intramuscularly as an oily solution, and the dosage is expressed in milligrams. Like œstrogen and androgen, progesterone is rapidly inactivated and excreted, but this is overcome to some extent in the case of œstrogen and androgen by converting them into esters, either benzoic or propionate, which delays their inactivation. Progesterone, however, differs from the other sex steroids in that it has no hydroxyl group in

its chemical composition, so that it is impossible to prepare an ester which would prolong its activity.

ETHISTERONE

Ethisterone is a compound prepared synthetically from either testosterone or progesterone, which is active orally. This compound is known chemically as pregneninolone, ethinyltestosterone or anhydrohydroxyprogesterone. Weight for weight, ethisterone orally has only about one-fifth to one-sixth the activity of progesterone parentally. The dosage of ethisterone by mouth therefore should be five to six times that of progesterone by injection. Norethisterone (17-alpha-ethinyl-19-norethisterone) is another orally active preparation which has recently become available. It is considered to have considerably greater progestational activity than ethisterone, and about half that of progesterone parenterally. All substances having a progesterone-like effect are collectively termed progestogens.

METHODS OF ADMINISTRATION

Generally, the progestogens are administered orally or by intramuscular injection. They can, however, be given intravenously or sub-fascially in the form of a pellet, or vaginally in the form of a pessary.

INDICATIONS FOR PROGESTOGEN THERAPY

Although progesterone is primarily a pregnancy or progestational hormone, and many claims have been made for its efficacy in the treatment of pregnancy disorders, it must be admitted that at the present time there are few, if any, disorders which can be consistently and successfully treated by progestogen therapy.

ABORTION

Threatened abortion.—The effectiveness of progesterone in the treatment of threatened abortion—a condition in which, theoretically, it should be of the greatest value—has not been substantiated; indeed some clinicians claim that progesterone may hasten rather than control an abortion. It is impossible to prognosticate in any case of threatened abortion as to the future of the pregnancy, as the outcome depends, for the most part, upon the degree of placental damage. When this is severe, no treatment can save the pregnancy, whereas in slight degrees, the bleeding generally responds to simple measures, such as rest and sedation. Nevertheless, it may be that in the future, when the more accurate techniques now available for hormone assay are applied to this important problem, it will be possible not only to assess the extent of the placental damage, but to estimate the degree of hormonal deficiency. When such information becomes available, the progestogens may prove to be of considerable therapeutic value in selected cases.

Recurrent abortion.—Much was expected of progesterone therapy in the treatment of recurrent abortion, and several series of favourable results have been reported. When comparable results, however, were obtained by a placebo, or by constant encouragement and reassurance, it became evident

that the effectiveness of the therapy was probably not due to the progesterone *per se*, but rather to the psychotherapeutic approach associated with its administration. This view is supported by the finding that once one pregnancy has continued to term after three or more consecutive abortions, subsequent pregnancies are generally uneventful.

REGULATION OF THE MENSTRUAL CYCLE

Progestogen combined with œstrogen is generally more effective in regulating the menstrual cycle, particularly when the intermenstrual phase is prolonged two or three weeks—oligomenorrhœa—than by giving either alone. The cycle can be regulated by giving ethinylœstradiol, 0.05 mg. daily, along with ethisterone, 10 mg. thrice daily, from the fifteenth to the twenty-fourth day of the cycle, counting the first day of menstruation as Day No. 1. This scheme of treatment is continued over three or four cycles and is then withdrawn.

DYSFUNCTIONAL UTERINE BLEEDING

Menorrhagia.—Regular but excessive menstrual loss preceded by ovulation is rarely due to an endocrine dysfunction. Nevertheless, it is claimed that the administration of progesterone daily for a few days preceding the onset of menstruation causes a reduction in the amount of blood loss. The results that I have obtained with this form of therapy have been so disappointing that I no longer employ it.

Metrorrhagia.—Excessive and irregular uterine bleeding occurring in the absence of ovulation—metropathia hæmorrhagica—is a true endocrine dysfunction, which is not uncommon. The essential disturbance is a failure of ovulation and corpus luteum formation. The administration of progesterone alone is effective in such cases, and a dosage of 10 to 20 mg. daily by injection, or 60 to 120 mg. of ethisterone by mouth, controls the bleeding within four to five days. The same dosage should be continued for a further five days after bleeding has ceased. Bleeding occurs within seven days of cessation of treatment, and is generally from a secretory endometrium. It is then advisable to give the same dosage daily from the 15th to the 24th day of the cycle, counting the first day of bleeding as Day No. 1. This scheme of treatment should be continued over three or four menstrual cycles.

This form of treatment has been superseded within recent years by a combination of œstrogen and progestogen. Although it seems paradoxical to administer œstrogen in the presence of abundance, the administration of œstrogen initially controls the bleeding more quickly than progesterone. The bleeding is due to a reduction in the blood concentration of œstrogen, and it can be controlled by raising the concentration above the level at which bleeding occurs. Various schemes of treatment have been advised, but the following has been found to be efficacious. Ethinylœstradiol, 0.05 mg., is given once, twice or thrice daily, or more frequently, depending upon the severity of the bleeding, and the initial dosage is continued daily for twenty-four days. During the last ten days of this treatment, i.e. from the 15th to

the 24th day, there is given in addition ethisterone, 10 to 20 mg. thrice daily. This therapy is followed by bleeding, which is associated with a secretory endometrium, within seven days. A second course of treatment should be started at the onset of the bleeding, but the daily dosage of ethinylœstradiol is reduced to 0.05 mg. daily, and is again continued for twenty-four days, with the addition of the same dosage of ethisterone during the last ten days: i.e. from the 15th to the 24th day. A third and similar course of treatment is advisable. This form of treatment has a twofold effect: (a) it controls the bleeding, and (b) it inhibits hypophysial activity and thus 'rests' the ovary. Withdrawal of the inhibiting effect on the pituitary is often followed by increased activity, adequate to induce full follicular maturation and ovulation. Recurrences do occur and further treatment may be necessary, but it is generally successful.

Another combination of progestogen and œstrogen has recently been introduced for metropathia hæmorrhagica; namely the intramuscular injection of a large dosage of progesterone, 125 mg., along with 10 mg. of œstradiol benzoate. Only one injection is given. This line of treatment is under trial, and the results so far have been equivocal; a large series of cases will have to be treated before its efficacy can be accurately assessed.

Œstrogen-progestogen therapy is most effective for metropathia hæmorrhagica in patients under the age of thirty-five. Metropathic bleeding, however, has its highest incidence in the pre-menopausal and menopausal years—a time when pelvic pathological lesions, particularly carcinoma, are more prone to occur. It is of the utmost importance therefore that at this phase of life malignant disease should be excluded and a definite diagnosis established by thorough curettage of the uterus, before instituting any hormone therapy.

SUMMARY

Progesterone is the naturally occurring specific hormone of the corpus luteum. It is also secreted by the adrenal gland and, in pregnancy, by the placenta. The hormone is metabolized in the liver and is excreted in the urine as several reduction products, the most important of which is pregnanediol—an inert substance. Ethisterone, a synthetic hormone, is prepared from either testosterone or progesterone. It is active orally but, weight for weight, its activity orally is only one-fifth to one-sixth that of progesterone parenterally. Any substance having a progesterone-like effect is termed a progestogen. Such substances have little effect on tissues which have not been simultaneously or previously primed by œstrogen.

Progesterone, although primarily a progestational hormone, has not been as efficacious in the treatment of pregnancy disorders as was at first anticipated. At the present time, it is probably of most value when combined with œstrogen, in regulation of the menstrual cycle, and in the treatment of metropathic bleeding.

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PRESENT AND POTENTIAL USES OF PARATHYROID EXTRACTS IN CLINICAL MEDICINE

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A RECENT renewal of interest in the structure and purification of parathyroid hormone makes timely a review of the present and potential usefulness of this hormone in clinical medicine.

AVAILABLE PARATHYROID PREPARATIONS

There is fairly conclusive evidence that parathyroid hormone is a protein. Available extracts, however, are electrophoretically non-homogeneous, and contain contaminating protein substances. The principal commercially available extracts at present are those manufactured by Eli Lilly and Company and by Parke, Davis and Company; these are supplied as sterile solutions for intramuscular, intravenous, or subcutaneous injection. The material is inactive orally. It contains 100 U.S.P. units per millilitre, this unit being defined as one-hundredth of the amount required to cause an increase of one milligram of calcium per 100 ml. of blood in a normal male dog weighing 8 to 16 kilograms, within 16 to 18 hours after subcutaneous injection. The Collip unit, more commonly used in Europe, is equal to 5 U.S.P. units. The inconstant hypercalcæmic response to crude extracts requires that no less than 10 dogs be used in the assay. The phosphaturic response to these extracts is even less constant, and is not used for the U.S.P. assay.

PARATHYROID EXTRACT IN THE TREATMENT OF HYPOPARATHYROIDISM

Parathyroid extract will reverse the chemical changes of hypoparathyroidism, but a number of factors limit its usefulness in the treatment of this condition. The lack of activity by the oral route is a disadvantage, as is the frequent occurrence of pain at the site of injection. More serious is the frequency with which the organism becomes resistant to continued administration. Antibody formation, either to the hormone or to impurities in the extracts, has been advanced as the cause of this resistance. When it occurs, it is usually after several weeks of administration. The objection that hyper-

calcæmia may be induced by overdosage should not constitute a major obstacle to its use in patients who can be carefully followed, although this hazard is increased by the variability of response to administration. The recommended dosage is between 20 and 40 U.S.P. units per day.

These problems, and the satisfactory response of individuals with hypoparathyroidism to treatment with vitamin D or dihydrotachysterol (AT-10) and calcium salts, have not encouraged the use of parathyroid extract. Vitamin D or AT-10 administration, however, is complicated in a significant number of cases (Litvak *et al.*, 1957) by the occurrence of hypercalcuria despite continued low or normal levels of the serum calcium. If more highly purified parathyroid extracts do not have the disadvantages of present preparations, they may find considerable usefulness in such patients. They would also obviate the necessity of giving the large number of pills of calcium salts which patients with hypoparathyroidism often require to supplement vitamin D or AT-10 treatment, and of their having to restrict milk in the diet because of its high phosphorus content.

In instances in which it is not clear whether hypoparathyroidism following thyroid or other surgery of the neck will be transient or permanent, the rapid effectiveness and dissipation of parathyroid hormone would make it an ideal form of treatment. It would avoid the frequent injections of calcium or the large number of pills which are often required; it would be preferable to vitamin D, which requires considerable time to become effective, and to lose effectiveness; which makes evaluation difficult and prolonged.

PARATHYROID EXTRACT IN THE DIFFERENTIATION OF TRUE AND PSEUDO-HYPOPARATHYROIDISM

The present clinical use of parathyroid extract is more or less restricted to differentiation of idiopathic and pseudo-hypoparathyroidism (Albright *et al.*, 1942, 1952; Elrick *et al.*, 1950). The former, in which the parathyroid glands are either absent or atrophic, is chemically indistinguishable from the latter, in which the glands are present and hyperplastic (and presumably hyperfunctioning), but in which the organism appears to be unresponsive to the hormone. Such differentiation is not required when hypoparathyroidism is obviously due to thyroidectomy, or when it occurs in association with moniliasis and/or Addison's disease (Sutphin *et al.*, 1943; Whitaker *et al.*, 1956). Since pseudo-hypoparathyroidism is almost certainly an inborn error, differentiation is also unnecessary when the onset is clearly in later life, although symptoms in some patients with pseudo-hypoparathyroidism may first appear at about the time of adolescence. Furthermore, diagnosis of pseudo-hypoparathyroidism is straightforward when short stature, the characteristic chondrodystrophy, and ectopic bone are associated with hypocalcæmia and hyperphosphatæmia. These changes, however, are genetically separate, and are not invariable findings in patients with the condition.

Differentiation between idiopathic and pseudo-hypoparathyroidism is of

considerable academic interest. If the observation of Litvak *et al.* (1957) that hypocalcæmic hypercalcuria does not occur in patients with pseudo-hypoparathyroidism treated with vitamin D or AT-10, is confirmed, it would also be useful. Treatment in this group could then be managed by the use of the urine Sulkowitch test alone (Albright, 1939), rather than by the frequent serum and urine calcium determinations which are required to rule out this complication in patients with other forms of hypoparathyroidism.

The diagnosis of pseudo-hypoparathyroidism can be established by use of the Ellsworth-Howard test (Ellsworth and Howard, 1934).

In this test, 200 units of parathyroid extract are injected into the fasting subject after three-hourly urine specimens have been obtained, following which three to five further specimens are collected, and the urine phosphorus excretion during each hour is measured. In the normal individual a three- to five-fold increase in phosphorus excretion may occur after parathyroid extract administration, whereas the rise may be as much as 10-fold or more in patients with true hypoparathyroidism, and negligible or nil in patients with pseudo-hypoparathyroidism. The inconstancy of parathyroid extracts and, as discussed later, the observation that recent extracts produce a lesser phosphaturia in normal and hypoparathyroid individuals than formerly, requires that a normal control be used each time a hypoparathyroid subject is tested.

Three or four daily injections of 200 units of parathyroid extract with measurement of the serum calcium before and after the series of injections may prove a more satisfactory test, but this approach has not yet been standardized.

THE DIURETIC EFFECT OF PARATHYROID HORMONE

Increased renal plasma flow and glomerular filtration are observed in hyperparathyroidism, and are probably responsible for the polyuria which is not accountable for by the osmotic diuretic effect of the increased urine calcium and phosphorus. Parathyroid extract has occasionally been used successfully as a diuretic but results have not been consistent. Handler and Cohn (1952) found that parathyroid extract given subcutaneously to dogs led to increased urinary phosphorus excretion almost solely by a decrease in tubular reabsorption, but that when given intravenously part of the increased urine phosphorus could be attributed to increased glomerular filtration and renal plasma flow. Whether an effect on filtration will be a significant action of purified preparations remains to be seen; that it is not a requisite to the hypercalcæmic or phosphaturic effects seems evident.

OTHER POTENTIAL USES OF PARATHYROID EXTRACTS

Consideration of other potential uses of pure parathyroid preparations requires a closer scrutiny of the hormone's mechanism of action.

Although there is no disagreement about the ability of parathyroid extracts to restore the hypoparathyroid state to normal, or to induce hyperparathyroidism, there remains considerable debate as to the sequence of events which occurs when parathyroid extract is given, and it is from observation of this sequence that many of the deductions have been made

as to the locus and mode of action of the hormone. According to Albright and Ellsworth (1929) and Albright and Reifenstein (1948), parathyroid extract in man leads first to an increase in urine phosphorus excretion, then to a decrease in the serum phosphorus, followed by a rise in the serum calcium and a subsequent rise in the urine calcium. This sequence of events led Albright to consider the kidney as the primary site of parathyroid hormone action, and subsequent work has suggested that this action is mainly to decrease the renal tubular reabsorption of phosphorus. According to this theory, lowering of the serum phosphorus disturbs the serum calcium-phosphorus solubility-product relationship and calcium salts are consequently withdrawn from bone.

A variety of other observations, including inconsistencies in this sequence of events under certain conditions and objections to the solubility-product concept (Neuman and Neuman, 1957), have led to the further conclusion that parathyroid hormone has, in addition, a direct effect on bone or on the relationship between the serum calcium and phosphorus and the bone salt. The debate at present is not whether parathyroid hormone acts directly on the kidney or on bone, but which of the two actions is more important. (For recent reviews of varying viewpoints, see Bartter, 1954; Greep and Kenny, 1955; Howard, 1956; and McLean, 1956.) There may be no simple answer to this question, and which action predominates may depend upon the state of the skeleton and of the body fluids with respect to calcium and phosphorus at the time when the hormone acts. Much of the present confusion may be due to giving equal weight to findings in different experimental animals, in which there may be differences of response to parathyroid extract.

An intriguing possibility, based on recent experimental evidence, is that the parathyroid gland may produce two distinct hormones, or that parathyroid extracts may contain one or more hormones and an artefact. Extracts have been modified by a number of workers in such a way that they lose their serum calcium-elevating effect while retaining a phosphaturic potency.

Stewart and Bowen (1952) incubated parathyroid extract with formaldehyde and found that the resulting material did not lead to a rise in serum calcium, but did produce phosphaturia. Similarly prepared extracts of spleen and thymus, however, had a similar effect in increasing urine phosphorus. The possibility is thus suggested that extracts may contain (and by inference that the parathyroid glands may produce) a calcium-mobilizing hormone (presumably acting on bone or on the relationship between bone salts and the serum calcium and phosphorus) and a phosphaturic hormone or artefact (which presumably acts to decrease renal tubular reabsorption of phosphorus).

The possibility of two hormones has been advanced (Munson, 1955) to explain the discrepancy between the greater phosphaturia induced by earlier preparations of parathyroid extract than by those being used at present, in the Ellsworth-Howard test. Munson has suggested that modifications in the method of preparation may have led to lessening of the phosphaturic factor with retention of the calcium-mobilizing factor. There have not, however, been significant changes in the preparation of Eli Lilly and Company's

extract, which is probably the main preparation used (Irwin, 1957).

Should two distinct hormones exist, their potential usefulness is only speculative. A hormone leading only to decreased tubular reabsorption of phosphorus would have a secondary effect on bone according to Allbright's hypothesis, unless dietary calcium is sufficient to meet the requirements for increased serum calcium and the consequent increased renal loss of calcium. It is, however, possible that phosphaturia could result from alteration of the relationship between intra- and extra-cellular phosphorus, without an effect on bone. Since the theoretical calcium-raising factor has not been isolated, it is impossible to predict what its over-all effect might be. If it led solely to bone dissolution it would seem to have no greater usefulness than other demineralizing agents; if its action is to alter the relationship between bone salt and the serum calcium and phosphorus, its effect cannot be predicted from present inadequate knowledge of this relationship.

From a limited practical viewpoint, whether there are one or two parathyroid hormones is secondary to the desirability of having a preparation for the treatment of hypoparathyroidism which would produce standard responses without pain at the site of injection and to which individuals would not become resistant.

From a broader point of view, the advantage of a pure parathyroid hormone or hormones would be considerable, and perhaps settle the long debate as to the action and mode of action of 'parathyroid hormone'. One can anticipate, too, that such a preparation or preparations might significantly increase our knowledge of bone metabolism in general, with perhaps widespread practical consequences.

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THE JAMES MACKENZIE LECTURE

TWENTY-FIVE YEARS IN COUNTRY PRACTICE*

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When I left Hospital nearly a quarter of a century ago in the pre-sulphonamide era and went to the country I seemed also to be moving back a whole generation.

AN OLD-TIME SURGERY

I joined an old doctor of 83 years of age, living with his wife in the dignified manner of another era and cared for by a staff that would make one envious today. In contrast to the dignity and comfort of the home, the surgery accommodation was depressing and entirely lacking in the amenities that we would now consider essential. The surgery was a room leading off from his smoke room; the walls were distempered in a dirty dark red; the floor was of bare boards, and the room ill lit by a small gas jet from his own plant. It contained a desk which was rarely used, half a dozen chairs, on one wall a dresser-like collection of shelves for stock mixtures, tinctures and ointments, all bearing the red label of the Society of Apothecaries, for no other drug firm would do, drawers for corks, instruments and other oddments. In front of this was a counter with a row of bottles, and jugs—some without handles—containing infusions of gentian, quassia, cinchona, senna and rhubarb, which had all been freshly prepared in the kitchen by the cook. There was no examination couch and no washbasin.

The contrast between the surgery and the home was difficult to understand, and yet the old patients adored him and gladly waited for hours, half a day or longer if necessary—sitting on a stone bench around the pump in the yard (fig. 1) if the weather was fine, or on the chairs in the surgery if wet—for the doctor whom they had known all their lives. As he was a parson's son this familiar quotation from Goldsmith is not entirely inappropriate:—

> 'A man he was to all the country dear,
> And passing rich with forty pounds a year;
> Remote from towns he ran his godly race,
> Nor e'er he changed nor wished to change his place'.

Across the yard were the outbuildings, the stables no longer housing his many horses. The coach house was occupied by a large Austin Saloon in which I was chauffeur-driven for the first three weeks; in another garage was a baby Austin.

AN OLD-TIME DOCTOR

As a student at the London Hospital the doctor had seen Lister; he remembered the filthy, stained frock coats of the doubting surgeons hanging up in

*The fourth James Mackenzie Lecture, delivered before the College of General Practitioners on November 16, 1957.

the surgeons' rooms; and he could recall changes as remarkable as those I shall describe. He had lived and practised from the same house for 58 years, and I doubt very much whether the surgery had changed in that time, or he himself. He had gone through all the major experiences of any old country doctor who was truly physician and surgeon. He liked to recall his surgical experiences and the major operations he had performed on kitchen tables. Of his little idiosyncrasies the patients told me much. After seeing his patient and coming downstairs, he would, if pleased, stand with his back to the fire, light his pipe and chaff the family. He was a great leg-puller. If he were worried, however, he would warm his thin cyanosed hands and immediately turn on his heel and walk out. He never discussed the condition of the patient with anyone, never gave a diagnosis and no-one would dare ask. He had the reputation for infallibility. This was the background to my new home.

FIG. 1.—Part of the old doctor's yard, showing the stone bench and pump.

MY INHERITANCE

When I arrived, agriculture was at a very low ebb, there was great poverty among the farming community, farmhouses were in need of repair, the old farm buildings filthy and tumbling down, and the labouring classes with large families lived in small cottages; they were poor and needy with the father bringing home about 18*s.* as his week's wages. Yet their families were private patients and obviously therefore fees were particularly small. Bills were sent out once a year, the response was invariably disappointing, for payments were rare, and one's financial reward discouraging to say the least. *Yet it did not seem to matter then.* An appreciable part of the practice was poor law, and many others had for years come under the indulgence of the doctor and never paid. The doctor is aptly described by Swift as a man—

> 'Who knows his art, but not the trade.
> Preferring his regard for me
> Before his credit, or his fee'.

This tradition I, too, inherited during the two years in which I lived in Victorian comfort with the old people.

My village was in the centre of the practice, with several other villages (fig. 2) within a radius of 12 miles; scattered throughout, and dotted fairly evenly over this large area, were small dairy farms worked by large families.

There were few big houses and few very large farms. Daily mileages of 50 to 60 miles were routine; often 80, and on occasions well over 100, miles have been covered. The nearest hospital was 10 miles away, and until 1948 almost all the acute surgery was done by G.P. surgeons, for the nearest

FIG. 2.—Cwmbach, one of the villages in my practice.

consultants were then 35 miles away. Nine-tenths of the patients were Welsh-speaking, and even today the medium of instruction in nearly all village schools is the Welsh language. Fortunately, I was able to speak fluently in the native tongue, and the patients immediately felt at ease with me, and I was supremely happy among them.

RURAL MIDWIFERY

In those days midwifery dominated one's life. Not having done an obstetric job, midwifery was a challenge and a constant anxiety.

I well remember soon after my arrival being sent for one Sunday morning to a cottage 10 miles away. I found a girl of 17 in labour whom I had not seen before. There was no district nurse. The case was a breech with extended legs. I remained with the patient all day. That night I called in a neighbouring practitioner to give an anæsthetic and with a great deal of trepidation, theoretical knowledge and good fortune, successfully flexed the legs and delivered a live child. I returned home about midnight.

Incidentally, afterwards she went to another doctor, and my fee to this day has never been paid. She has long since come back to me and I have forgiven her.

There were few district nurses in those days and I was obliged to attend all the confinements looked after by handy women. In this way I rapidly acquired experience and skill, though often in difficult circumstances. The

greatest difficulty on these occasions was to contend with the relatives, especially 'granny', and to withstand the plea 'Can't you do something, doctor?'. My answer was always, though alas much less often today, 'the more you do, the less you do' and, for extra emphasis, 'the less you do, the more you do'.

The one outstanding quality necessary for a successful midwifery practice is sound judgment—knowing when to leave things alone and knowing when to time your interventions; the temptation to do a forceps delivery and hurry things on when you are miles away and the day's work is ahead of you is very strong. The use of forceps grows less as one's experience grows greater. Looking back on those days, I seem to have spent a great deal of my time delivering cases, mostly at night. There was little antenatal care, except among the few more enlightened people, and I was constantly being sent for to confinements which were really emergencies. One usually gave the anæsthetic as well as doing the delivery, for calling another doctor for an anæsthetic was apt in those early days to give patients an impression of inexperience or even incompetence in dealing with midwifery.

Yet with all its anxieties, and they were great, midwifery performed under conditions which would not be tolerated today, gave immense satisfaction and pleasure. The sense of achievement outweighed all other experiences in general practice. The delivery of each baby by the family doctor in the patient's home, forges a link with that family which binds the doctor into their lives. This is something that we are beginning to miss today.

As one might expect, since there was so little antenatal care, severe toxæmia of pregnancy was commoner than today. It is astonishing how ill an expectant mother would allow herself to become before calling in her doctor. I saw several true eclampsias, two of whom lived a long way from the road and presented great difficulty in transferring to hospital. Although regular antenatal work has now made a difference, there is much still to do.

The risk of puerperal sepsis heightened the anxieties of midwifery when undertaken under primitive conditions in cottages. The fear of that dreaded complication, which was often spoken of by patients, compelled us to exercise the greatest care with our aseptic technique. Yet cases involving internal manipulation and forceps delivery, though without gloves, rarely went wrong.

The one case of fulminating puerperal sepsis which I saw, and which ended fatally, was a normal delivery by the district nurse in a cottage. I was called in on the fourth day and found the mother critically ill and delirious, with a temperature of 104° F. (40° C.). In bed with her were two young children suffering from impetigo. She was admitted to and died in the isolation hospital.

TRACTOR-TRACTION

Such experiences fall to the lot of many town doctors, but the following incident could only occur in the country.

One night, leaving a farmhouse after a confinement, I found a number of farmers gathered around the door of the cowhouse, in which a cow was mooing distressingly and failing to calve. The farmer had tied a rope around the forelegs of the calf and

was actually attaching the other end to a tractor. A new method of delivery by tractor-traction was about to begin. The procedure horrified me and I pleaded to be allowed to examine the cow. This I did, for the first time in my life, and found an extended head which I was able to push back; flexion was then easily performed and delivery effected.

I returned to bed that night feeling the night's work had been well done.

LOBAR PNEUMONIA

Whenever I think of children's disease I associate it with Sir Luke Fildes's picture, 'The Doctor'. An artist's proof copy of it hangs in my hall.

Few are unfamiliar with the scene it depicts of the distinguished-looking, bearded family doctor, chin in hand, leaning forward watching a child critically ill in a small bare living room of a poor country cottage. The lamp shines on the faces of the doctor and the child, and in the background the face of the anxious father and the head and shoulders of the crying mother. The night has been long and the crisis is imminent, the doctor watches patiently, comforting the mother by his presence but unable to help the child, who by now is entirely unaware that he is there.

The picture so clearly typifies the work of the old family doctor; and it is this situation that I often recall as if in a bad dream. It occurred so often in the early days. The anxiety weighed heavily upon the family doctor; the twice-daily visits; the attempts to convey a calm reassurance that gave hope and confidence. How difficult it was to preserve Osler's 'equanimity'. I think it fair to say that the younger generation is unaware of the constant worries and anxieties which *never* seemed to leave us.

The work involved and the anxiety attendant upon cases of lobar pneumonia are vivid memories. Two or three cases of lobar pneumonia occurring simultaneously in a scattered country practice could keep one on the road from morn till night. Twice-daily visits were essential until the crisis occurred, generally on the ninth day. Successful treatment consisted in constant observation, careful nursing, treating the patient symptomatically, and alleviating the anxiety of the relatives. In those days the mortality was considered to be between 10 and 20 per cent., but I feel that the former would be a fairer assessment, though I wonder it was not higher under the prevailing conditions.

Imagine a small, crowded, low-ceiling'd room, its small window tightly shut and perhaps impossible to open, a patient dressed in a vest or two and a thick Welsh flannel shirt soaked in perspiration (and which would remain unchanged until perspiration ceased, probably after convalescence), layers of heavy home-made quilts surrounding him, and near the bed one of several women poised with a linseed meal poultice freshly prepared and ready to apply. With relays of kindly women neighbours all correctly dressed in white aprons, this went on throughout the whole illness. This scene always faced me on the visit after pneumonia had been diagnosed. I endeavoured gradually to alter this pneumonia routine which had been so rigidly imposed by the orders of my predecessor whose skill in inflammation of the lungs they all remembered. Faced with it I could but try and assess the clinical condition and discuss daily the prognosis with various members of the family. Believing in optimism, I endeavoured to give a good prognosis

which would encourage the family to keep going day and night in their difficult task. A bad prognosis would have made it more difficult for them to carry on and some would have found it impossible. In theory, the outcome was influenced by the age of the patient and the conditions, yet it was surprising how many survived however bad the conditions might be. Success, of course, was credited to the medicine, brandy *ad lib.*, and linseed poultices; any advice to sponge the patient and change his clothes was, as a rule, rigidly resisted.

How difficult some of these situations were for a young doctor, when all the family listened to the assessment of the case. A bad prognosis upset the household and a guarded one often gave rise to doubts of one's ability, as did a request for a second opinion. In the course of time I have seen so much unnecessary distress caused to families by an unduly guarded and pessimistic prognosis due to a doctor's desire to be on the safe side. I consider it to be our duty as family doctors to carry our anxieties in our own hearts, and not needlessly transfer our fears to those less equipped to bear them.

HEART FAILURE

In my early days in practice the emphasis in treating cardiac failure was on prolonged bed rest and digitalization. With the onset of œdema, irreversible in those days, the commonest procedure was acupuncture by means of a small scalpel or even Southey's tubes, a legacy of my predecessor.

The incidence of cardiac asthma, as we used to call it, was far higher than today. It accounted for numerous and regular night calls.

I well recall the first of these: a big heavy man sitting on the side of the bed as blue as a plum, *in extremis* from acute pulmonary œdema, with blood-stained fluid pouring out of his mouth into a chamber on the floor. I quickly tied a rubber catheter around his arm and with a scalpel slashed into his vein—the blood shot out, hit my face, covered a white cricket sweater I was wearing and then shot out over the wall behind me and even splashed the ceiling. A couple of pints and more were quickly collected into a basin and the relief was dramatic. In a matter of ten minutes he was a different man, breathing easily and talking freely, and with gratitude. For two years he sent for me regularly at night and I often did a venesection with a French's needle and a rubber tubing.

Ever since then I have been a great devotee of the bleeding cult.

THE ACUTE ABDOMEN

For a young doctor starting practice the acute abdomen is always a challenge, since failure or delay in diagnosis will have repercussions that will echo and re-echo through the practice to one's detriment. It is the sense of urgency that creates the worry and these cases brook no procrastination or lengthy cogitation—the challenge is immediate. The threat to life entailed in the failure to make an early diagnosis in an acute abdomen recurs more constantly than in any other emergency. The only way to prepare for it is by holding a surgical appointment in hospital. In our practice, in the five years from 1946 to 1950, out of about 7000 patients, there were 128 acute abdominal cases, including 87 appendices, of which seven had perforated, and the

remainder spread over 12 conditions, giving an incidence of acute emergencies of 0.35 per cent. per annum, and of acute appendicitis of 0.24 per cent. In my own series of cases in the ten-year period, 1941 to 1950, there were 43 cases of appendicitis in a total of 72 emergencies, giving a proportion of 60 per cent.

In a remote rural practice in the old days there were few opportunities for obtaining a consultant opinion. Distances almost inevitably meant unjustifiable delay. I resolved that if I felt a case was an acute abdomen at my first visit I would send it into hospital immediately, and neither fields nor floods, neither families nor friends, should interfere or delay the patient once I made my diagnosis. Parents and relatives learn to trust in one's opinion and advice, and appreciate a readiness to take firm responsibility.

TRANSPORT PROBLEMS

Transport was always difficult and a source of anxiety in the country but the ambulance service has solved this problem. In the early days I nearly always took my own patients into hospital, especially at night and always in cases of perforation. I enjoyed doing this, for then I could assist at the operation and compare the clinical picture with the operation findings. The following incident was typical of many like experiences.

I was called about 1 a.m. to a woman with acute gall-stone colic. I gave her half a grain of morphine and, while waiting to ensure that this took effect, I sat down in the kitchen with the husband, who complained quite casually about his indigestion and said he really must come and see me about it. I eventually got home, went to bed and off to sleep. About 4.30 a.m. I had a telephone message once again from the son who, in an agitated voice, asked me to come up immediately because 'something terrible had happened to father'. I leaped out of bed, frightening my wife in the process, and said 'this chap's got a perforation'. It was soon confirmed and I gave him ¼ grain of morphine, put him in my car and took him 16 miles to hospital. At 7.30 a.m. I was assisting at the operation. I had travelled 39 miles for that little family during the night.

Accepting responsibility for transport is not without its reward, for this patient provided me with my Christmas turkey for many years afterwards.

There is, of course, the occasional patient one meets with in a rural practice who refuses to be transported.

Within a few weeks of entering practice my old predecessor took me to see a farmer aged 68 whom he had been attending for a fortnight suffering from a large growth of the cæcum. I thought it was a large appendix abscess filling the right iliac fossa, for there was a suspicion of redness and œdema of the skin of the abdominal wall. The patient refused to go into hospital although his daughter, a theatre sister in a county hospital, who was called home, tried to persuade him. He agreed to have any other treatment. I asked the old doctor to give an anæsthetic, which he did, using chloroform on an open mask. I made a small incision through the skin, and put in a large trocar and cannula attached to a Potain's aspirator and took out 3 pints of thick pus. The right iliac fossa collapsed, the temperature settled and the old farmer immediately got better. He was up in ten days and in no time was driving his trap to market again, little realizing that his debt to Providence was greater than to me.

Seven months later I had a telephone message one Sunday morning from a surgeon 60 miles away, saying that this farmer was on holiday and had an acute appendix, but he refused to go into hospital unless I came up and told him to. I felt it was my duty to go. I persuaded him to have his operation, at which I assisted.

We found a typically inflamed œdematous appendix with a fæcolith near the tip; in addition, attached to the appendix there was an unusual structure in appearance exactly like a collapsed toy balloon—apparently the old abscess wall. It was past midnight when I returned home and, though tired after another long journey, felt rewarded, though neither then nor subsequently financially so.

MISCELLANEA

Cases of retention of urine were always a burden and anxiety. Here, too, occasionally there was difficulty in persuading an old man to enter hospital. There was no alternative but to catheterize twice daily or, if the distances were exceptional, to tie in a catheter. I remember going 7 miles night and morning for six weeks to catheterize a patient who would not tolerate an indwelling one. These cases added considerably to one's work.

Infections of the hand and arm remain in my memory because of the appalling results of delay in seeking medical advice, due to the patient having meanwhile endured various country remedies. Many of them had osteomyelitis of the fingers, vascular necroses and sequestra of the phalanges which caused great subsequent disability and disfigurement. The treatment was often a ruthless incision under an ethyl chloride spray, with the hand placed on a towel on the corner of the desk. Occasionally amputation was necessary.

Quinsies were much more common than they are today and occasionally so severe as to endanger breathing and life. An immediate incision over the pointing abscess was often safer than leaving it until the next morning.

Cases of varicose ulceration of the leg were numerous and all those who had them resisted any suggestion of cure. They had endured them for many years and were convinced that if they healed a discharge would break out elsewhere. One old lady of 83 had suffered her ulcer for 47 years. I was able to heal this for her by injecting her veins and occlusive bandaging. She lived another five years after that in comfort.

Road and farm accidents took up a great deal of time and energy. With no ambulance service and few cars, emergency treatment for arrest of hæmorrhage and suture of wounds was performed in fields and farmyards or on the verge of a roadside. Every road accident meant a call for a doctor and the patient was not moved until the arrival of the doctor, however long delayed this might be.

Every day brought its emergencies, anxieties and challenges that thrust their responsibility on me, a young man then practising on my own. Had I not done any house jobs it would have been impossible for me to bring the amount of confidence to my work that I did, though I fully realized my limitations. If truth be told, although people liked to think that the young doctor had modern drugs and methods, my resources did not differ much from those of my predecessor and my black bag was almost as bare as his had been.

THE PERIOD OF REVOLUTION

Such was the state of general practice when, suddenly, the dramatic news

came from Germany that Domagk had discovered a chemical called 'prontosil'. I shall never forget the circumstances. It was in 1935, while I was still living with the old doctor, that I read at night by the aid of a solitary candle on my pillow a brief account of this new drug, and its significance brought a new light into the darkened bedroom. It was unbelievable that a drug had been found which would cure puerperal sepsis. I had not been conditioned to accept the miraculous as those of a younger generation have accepted penicillin and the new antibiotics. This to me and to others of my generation was a miracle, and we were awestruck by its significance. On reflection I still consider this the great divide in therapeutics, the turning point in the treatment of infectious disease.

And this brings us to my second period—the period between 1938 and 1948—the Period of Revolution for it did truly mean that, both therapeutically and politically.

The discovery of the sulphonamides brought such a fundamental change in therapeutics that treatment was changed from expectant to active, and we began to experiment with the unknown. Overnight almost, a series of conditions that were virtually untreatable came within the power and scope of every family doctor. In the decade, 1934 to 1944, deaths from pneumonia were reduced by half. This was a period that brought great joy to us; it was exciting to have a sword in one's hand to deal with the enemies that had decimated man for so long.

THE PUBLIC HEALTH LABORATORY SERVICE

With the sulphonamides, the greatest boon to us was the establishment, in 1940, of the emergency public health laboratory service (fig. 3) under the Medical Research Council. It gave us the greatest help, cooperation, and advice in all epidemiological matters, as the following incident shows.

Scarlet fever broke out suddenly in one of the village schools in January 1946; out of 95 pupils there were 11 cases within a few days. With the permission of the county medical officer of health and the school medical officer and the cooperation of the director of the emergency public health laboratory, my partner and I took nose and throat swabs of all the children present. We picked out 28 throat carriers, 11 of whom also had a heavy 4-plus infection of the nose of group 'A' hæmolytic streptococcus type 20. We excluded these children from the school and demonstrated to their mothers how to treat them with sulphathiazole snuff. We insisted on the nasal carriers having two negative swabs before returning to school. Not a single case of scarlet fever developed after this.

About a month later, the infection broke out with six cases in another little school of 47 pupils in the village. We found 14 throat carriers among them, nine of whom were also nasal carriers. We adopted the same treatment and stopped this epidemic too. No special cleaning of the school or disinfection of clothing was carried out. Within a few days one case occurred in another school. The source of infection was a child who had been away, and transmission occurred in a Sunday school class. These were dealt with promptly, with no further cases.

After this successful experiment in preventive medicine, our example was followed by public health department teams when outbreaks occurred later on in grammar schools in the county.

A country partnership, of course, is in an exceptional position regarding

the children in schools, for all of them are patients of one or other of the partners. They all belong, as it were, to the same family, and we assume the responsibility for them. This would be impossible in a county town or urban area.

Four cases of rheumatic fever—two severe and two mild—were the sequel to the outbreak of scarlet fever among the children in the first school. One of the severe cases picked up her streptococcal infection about a week before we did our swabbing; the other was at school. Unfortunately both are now dead: one died of rheumatic carditis a year later, at the age of 7, and the other died this year, aged 16, after years of invalidism. She had one of the largest hearts and the worst chest deformity I have ever seen. I have often wondered how many more would have succumbed to rheumatic fever had the epidemic been allowed to spread through the school. The mortality rate of 2 per cent. in one school is too high, and it is reasonable to suppose that the high annual national incidence of between 3000 and 4000 cases of rheumatic fever, accepted by the Medical Research Council, could be cut down if more effective measures were taken.

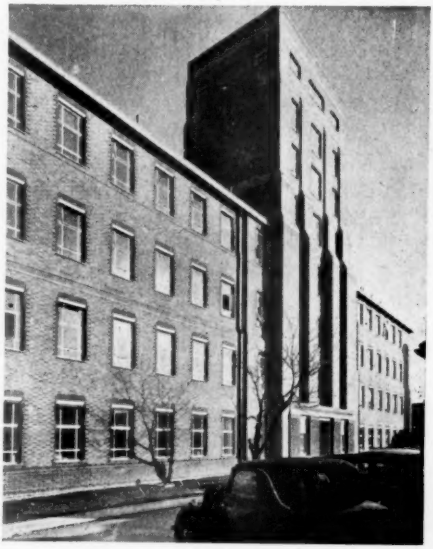

FIG. 3.—Central Public Health Laboratory, Colindale.

Another case illustrating the prompt cooperation of the laboratory service was one of Weil's disease in a miller aged 64.

> I obtained a sample of his blood on a Wednesday afternoon, and took it myself 20 miles to the laboratory. On the following Friday afternoon I was rung up and told that the diagnosis was confirmed, the blood having meanwhile been sent to Oxford and the result obtained in 48 hours. I attended this man twice daily for about ten days, covering 44 miles a day, giving him intravenous gluconates, glucose and saline plus anti-serum. This was before penicillin became available. Eventually my account was presented, and on visiting him I noticed on the little wicker bedside table a sum of money awaiting me. I told him that he need not pay the whole amount at once, but he answered me in Welsh: 'Doctor Bach, if it were not for you I wouldn't be here, and my widow would have had to pay twice this amount to the carpenter, and I wouldn't have been here in the end'.

The director of the laboratory and his assistant encouraged us to visit them and discuss our cases and by them we were taught to become bacteriologically minded. We became alive to our new responsibilities in cases of P.U.O. and in investigating isolated outbreaks of diarrhœa which were so

often a Sonne dysentery. We were taught that in future the swab and the specimen bottle were to become an essential part of the equipment in our bag, and we quickly realized, too, that it was more profitable to take the specimens to the laboratory than to send them. I have no doubt that the coming of the laboratory into our midst helped us to become better doctors.

FIG. 4.—Our Surgery.

FIG. 5.—A corner of my consulting room.

THE NATIONAL HEALTH SERVICE

Soon after the National Health Service began it became obvious to our partnership that a reorganization of our practice would be necessary to meet the increased demands on our time and energy. Instead of working from our own houses we decided to build a new surgery (fig. 4) in the centre of the village on a piece of waste ground littered with stones from the ruins of The Coach and Horses. We employed our own patients to build it, and started work there on May 1, 1950. The accommodation included a waiting room, an office, two consulting rooms (fig. 5), a minor surgical theatre and small dispensary, and a cloak-room, with a parking ground for our cars. The theatre has an operating table with the upper and lower third adjustable, glass instrument cupboards and, of course, a sterilizer. Dressing drums are sterilized for us at the hospital. We have a Portanaest gas and oxygen machine. From this well-equipped surgery we have derived the greatest pleasure and satisfaction in clinical cooperation and consultation, and we believe that the standard of our work has been improved. The extent and scope of our minor surgery are illustrated by the following figures which, I feel sure, are representative of similar work in most rural partnerships throughout the country. In the five years from 1950 to 1955, 166 minor

operative procedures involving some form of anæsthesia were undertaken 85 of these with gas and oxygen. Accidents needing one or more sutures totalled 116. A number of these, especially in the case of children and needing one or more sutures, were done under a local anæsthetic, a procedure well worth the extra trouble. I think it is fair to say the amount of minor surgical work done by our practice considerably eases the burdens of the hospital and ambulance services. In addition to covering most of the common conditions, we still do our own injections for varicose veins.

GROUP PRACTICE

Most farmers have cars and we encourage patients needing special investigation or treatment to come to the surgery, where they can be examined more efficiently, and without the sense of urgency that is unavoidable on a busy round. Cases of acute otitis media seen on a round have been brought to the surgery for myringotomy that evening. The proportion of visits to surgery attendances is still higher, however, than in an urban practice, and this is always likely to be so, especially with an ageing population. In my opinion a likely trend in group practices in the future will be consultations by appointment throughout the day, with one or more partners doing the visiting. More expensive equipment such as an electrocardiograph and other items would then be a justifiable innovation. These trends have already occurred in many group practices and should be encouraged.

We still do such procedures as paracentesis abdominis.

I have one patient with a calcified constrictive pericarditis who had a cardiac decompression done in London in 1944. At that time the operation, which, incidentally, I was able to attend, was the 22nd of its kind performed in this country. Until six months ago he needed regular injections of mercurial diuretics and also periodic paracentesis, at which a bucketful and more was drained at a time. Strangely, he has recovered from his failure and has now neither ascites nor œdema.

Anxiety states and endogenous depressions are not common in rural areas, but when they occur they are clearly hereditary and a knowledge of the family history confirms this. The population in a rural practice is more or less static and this simplifies the understanding of familial weaknesses.

Midwifery has greatly changed in character. Antenatal work is done more efficiently than ever before and nearly all patients attend regularly. Contrary to expectation, more patients are delivered in hospital. There are two reasons for this: one is the social trend and the other the obstetric reason that patients think they are safer in hospital where nearly all primiparæ are now delivered. Lack of help on the farms and the impossibility of obtaining home helps have been chiefly responsible for this change which has occurred with a snowball effect over the last few years. Even when at about the 39th week, with the head well down and the outlet normal and indicating an easy delivery, and it is obvious that transport to hospital in labour is not without its risk, the patient still elects to go into hospital. She is sometimes discharged home in two or three days under the care of the district nurses, who feel increasingly frustrated and disappointed with their diminishing responsi-

bilities. In our practice the proportion of hospital to home deliveries is equal.

Occasionally, difficult decisions have to be made in rural practice.

One morning a few months ago I saw a woman, 32 weeks' pregnant, who was severely shocked and the possibility of an internal accidental hæmorrhage had to be considered. I sent for the ambulance and the flying squad, but soon it was clear that she had had a pulmonary embolism. I weighed things up carefully and decided it would be fatal to move her. I sent the ambulance away. She remained on continuous oxygen and intravenous heparin six-hourly for three days. The night work was shared between the partners. After five days the crisis was over and she was removed to hospital.

This sort of cooperation is one of the privileges of a partnership that benefit the patient, and I agree wholeheartedly with Dr. Stephen Taylor's impression that doctors in a successful group almost always supply a better medical service.

A WAY OF LIFE

From this somewhat discursive chronicle of my early days, with their difficulties and problems, some of my fellow-practitioners may agree with Canon Sydney Smith, who said cynically 'I have no relish for the country; it is a kind of healthy grave', and wonder what made me stay at my self-chosen post for such a long stretch of time. To live in the country you must love the country and to practise there, is a way of life. The compensations are many: the changing picture of the seasons, the succession of Spring flowers in the hedgerows, the sight of the crying seagulls as they follow the tractor along the glistening freshly ploughed furrows, the sight of a pedigree herd of shining Friesians grazing, the smell of new-mown hay and the view from a hilltop of the countryside and its farms, and the warmth of the feeling of being a part of it all. And then in leisure time the pleasures of trout fishing with varying success and the gift of a basket of trout or a sea trout from a more skilful fisherman, or the poached salmon in winter surreptitiously placed in the boot of the car by a grateful patient. The winter afternoons with dog and gun, trying to bag the elusive woodcock or the darting snipe, and the occasional evening's duck flighting. And above all the constant kindness of patients with gifts of farm produce. All these form part of the country pattern—need it be wondered why I stayed? Does not Kipling strike the target with the lines:—

> 'God gives all men all earth to love,
> But, since man's heart is small,
> Ordains for each one spot should prove
> Beloved over all'.

The fan-like parcel of land drained by the river Taf and its half-dozen tributaries which contains our practice still retains today, as the Rural Deanery of St. Clears, the very shape it had 700 years ago as the Norman lordship of St. Clears, and 700 years before that as the tribal Cantref (or Hundred) of Gwarthaf in the land of Dyfed. It has become for me the spot ordained, beloved over all, where it has been, and still is, my privilege, with a united body of colleagues to practise the art of medicine. And if I had the choice all over again I could not wish it to be otherwise or elsewhere.

GENERAL PRACTITIONERS' FORUM

INFLUENZAL IMPRESSIONS—1957

By J. B. WILSON, M.D., M.R.C.P.Ed.
Lochmaben, Lockerbie, Dumfriesshire

Now that the influenza epidemic is waning, it may perhaps be helpful to note some of the lessons to be learned from it. During the past months, the clinical picture in the different forms seen in various groups and ages has become all too familiar, although fortunately in this area its ravages, albeit widespread enough, have not been too severe and there has usually been some time to spare, even if only while driving between country calls, to ponder over its oddities.

RECURRENT ATTACKS

The first of these was that a small proportion of patients were unfortunate enough to have two apparent attacks of influenza at intervals of about ten days. Having recovered from one bout and returned to work, a second attack once more laid them low. Perhaps one of these illnesses was misdiagnosed, but it may have been that these unfortunates were the hosts to two different strains of influenzal virus.

Gastro-intestinal upsets.—As usual, the pattern of the disease tended to differ in the younger children. In them the upset was confined largely to the upper intestinal tract. Adults, however, were not immune from this form of the disease, for after severe sickness and abdominal pain, accompanied by severe prostration, two patients went on to pass obvious melæna motions, arising presumably from a severe toxic gastritis.

ORAL PENICILLIN

During an influenza epidemic, when time is at such a premium, clinical experience may have to take the place of the full laboratory and radiological investigations, and in this connexion the use of oral penicillin preparations in young children, who have not responded promptly to the usual symptomatic treatment, is worthy of mention. These youngsters with a troublesome cough, anorexia and striking drowsiness, even in the absence of any clinical signs in the chest or elevation of temperature, responded in a way little short of miraculous to a few days' treatment with oral penicillin. This fact, taken in conjunction with the better-known clinical picture of pneumonic consolidation in adults, was thought to indicate that there might be a similar lesion in these children. Corroboration of the usefulness of these preparations was obtained in one little girl who did not respond by the usual rapid

improvement and who was found to have missed many doses of penicillin when her mother omitted to waken her at medicine time from her nearly continuous sleep. Once this detail was rectified, recovery was rapid. On the other hand, the danger of drawing conclusions from clinical impressions was underlined when opportunity was taken to have the little patient's chest x-rayed and no radiological changes were demonstrated.

General practitioners have realized for some time that the old-fashioned dramatic picture of lobar pneumonia has vanished from our midst and that its place has been taken by a more insidious illness, the spotting of which demands eternal vigilance from all. Its presence can be suspected in any patient suffering from a respiratory infection lasting more than a few days, or one presenting with any atypical symptoms—especially that of pleural pain, however transient its nature. In these cases, the clinical findings of pneumonic consolidation are completely absent in the early stages and it is only when the patient is clinically improving that they become obvious. This is the stage when the patient first comes under the observation of the chest physician, who doubtless wonders how such obvious clinical findings have been overlooked.

THE IMPORTANCE OF FLUIDS

The traditional treatment of influenza lays stress on the prescription of hot sweet drinks and plenty of fluids. The importance of seeing that these instructions are carried out was emphasized by the occurrence of two cases of severe renal colic. Presumably this complication arose because of the widespread nature of the epidemic, which served in these two patients to bring out a latent tendency to stone or crystal formation. It does, however, underline the necessity of forcing fluids in those illnesses in which sweating is a feature.

CONCLUSION

The drawing of conclusions from a small series of cases may occasionally produce wrong impressions but, after all, is it not in this way that most clinical experience is gained, and such clinical experience is one of the older practitioner's most valuable assets. The important point is that, while his critical faculties are being given full reign, his experience should be backed up by frequent consultations with his colleagues and a continuing knowledge of the basic advances in the clinical field.

SECTION OF GENERAL PRACTICE OF THE

ROYAL SOCIETY OF MEDICINE

DISCUSSION ON THE MANAGEMENT OF THE HOPELESS CASE

November 20, 1957

Dr. Ronald Gibson (*Winchester*).—Total care involves not only the patient. His environment and his relatives have also to be included. The family doctor sets the stage and trains the supporting cast so that the personality, idiosyncrasies, foibles and the hopeless disease of the patient can be looked after to greater effect.

THE ENVIRONMENT

The design of the environment depends upon two major factors at the outset: the home background and the financial status. The Welfare State has influenced both of these. It has raised the standard of living of the population, eliminated gross poverty and improved public health education. Thus the National Health Service doctor can enter practically every home in the country, and can take with him the state nurse, the health visitor, the home help, the social or welfare worker, without any thought for the family's income. Nowadays therefore the degree to which these people can influence the environment depends more upon whether the patient is surrounded by a loving and responsible family than upon the financial or social status of the family, and it is unfortunate that the State in taking so much obligation upon itself for the welfare of society has, at the same time and inevitably, lessened individual responsibility towards the family. Without this individual responsibility even a healthy family may break down, and it is certain that one which includes a chronic sick person will tend to push the responsibility for care and management on to the State, and the patient's environment will be that of a chronic sick hospital or nursing home.

Attention to environment obviously involves in the first place a rearrangement of the house—not always easy to bring about at once—often a great deal of suggestion is required over a long period. A bedroom downstairs may mean considerable sacrifice to some families; with others there will be room to spare. Some patients—particularly the older ones—fear the ground floor at night. Such a move may also necessitate the provision of lavatory accommodation downstairs, the elimination of steps in and outside the house, the widening of doors and gates, and so on. In this re-educating and conditioning process the health visitor can be a great help to the doctor.

So many 'gadgets' can be invented and provided, which will cover almost any individual's requirements. The environment plays an important part in building up the pattern of the patient's day—not only to keep him amused

and occupied in gainful occupation, but also to impress him continually with the true fact that he can still be a useful member of the community.

Diversionary activities designed to take the patient's mind off himself and his illness include the television and wireless, crossword and jig-saw puzzles and various card games; the encouragement of hobbies, such as carpentry, painting and needlework, writing and stamp collecting. All these fall within the province of the social and welfare workers, the W.V.S. and the Red Cross. Not to be forgotten are visits from the librarian, and, perhaps most important of all, the arrangements for continuing the patient's education, particularly along the lines necessary for possible re-employment. People play a prominent part in the make-up of the environment, and I would stress the importance of introducing new friends to the patient, of ensuring his association with young people and of maintaining at all costs his personal vanity.

THE RELATIVES

I am reminded of the young general practitioner who, after a misdiagnosis and subsequent death of his patient, felt it incumbent upon himself to apologize to the relatives for his shortcomings. They were quick to reassure him. He was, they said, the only one who had given them any hope. Where possible it should be left to the family doctor to deal with relatives. This is not intended as a slur on the consultant; I always pity him when he has to interview relatives in hospital—he has probably only known the patient for a few hours, and he meets the relatives face to face for the first time outside the ward. How can he possibly know how much to tell and how much to leave out, and, particularly, how much of the future to predict?

It is therefore the G.P. with a knowledge of the family extending over years, who best knows how to manage these people. Mis-management of relatives means mismanagement of the patient, for the hopeless case is going to be far more dependent upon them than on the doctor or his helpers—it is therefore vital that the right outlook should be adopted from the start.

THE PATIENT

I am convinced that from the very outset it is the family doctor's duty to encourage the patient in an aggressive attitude to his disease. Along with this must obviously go the exploitation of every available means to procure even temporary and partial remission of the disease. Both of these—the aggressive attitude and the attempts at treatment—are calculated to encourage the patient to a positive attitude towards his illness—in other words, a hopeful attitude.

The essence is that the onset and progress of a disease must never be permitted to interfere with the patient's love of life. He may love it from a bed or a chair, a bedroom or a ward, but the changing circumstances of his life must not interfere with his devotion to it.

Which leads me to my next point. I have often found it useful to remind newly diagnosed hopeless patients that, if they come to think of it, life is

always a struggle—even for the apparently healthy individual, and either mentally, physically, or both. The onset of an incurable disease may add to the struggle but may not bring it up to the level of that suffered by some people who, though apparently healthy, yet are constantly fighting some unseen physical or mental disability which they dare not share with anyone.

The social worker is an invaluable member of the doctor's team. It is beyond the time and the ability of the average family doctor to analyse the vocational capabilities of the patient. The analysis, however, must be done. Work need not necessarily be for financial gain. It may merely be for mental relaxation; as a time-passer or (perhaps most important of all) as a means of doing service to others in the community.

SPIRITUAL THERAPY

It has always seemed remarkable to me that most patients automatically regard their doctors as atheists or, at best, as agnostics. Many times I have regretted that a patient should feel it necessary to apologize to me for the suggestion that he might get some help from a priest—and would I mind if he tried. Worse still is the surreptitious consultation between patient and parson without letting the doctor know, in case he would be offended or would not understand. I include spiritual therapy automatically in my care of the hopeless case, and only if I receive a dogmatic refusal of such help do I pass over it. I am convinced that a patient on whom it is not possible to apply spiritual therapy is missing a major part of his treatment, and the lack of this vital constituent of total care makes the remainder far more difficult to apply and far less effective in result.

One cannot leave this aspect of care without touching on the tragic move so often made by patients or their relatives who, in desperation at the hopelessly inevitable nature of the prognosis, proceed to employ some peculiar and unorthodox 'spiritual aid', of which there are so many different varieties. That some of these so-called spiritual healers, or the like are honest in their beliefs and in their desire to help there can be no doubt, but others merely exist in order to play on the feelings of, and to make money out of, the hopelessly ill. All one can do is to wait for the anticlimax and, when it comes (as it inevitably must), receive the patient back into the fold without recrimination. Argument in the beginning or recrimination at the end may bring about a change of doctor, and with this a possible change in the routine of daily life and of treatment. This should be avoided at all costs (even that of the doctor's pride) for enough damage may well have been done without this additional risk.

THE PHASE OF DYING

The fundamental aims at this stage are the banishment of pain and anxiety. A judgment of the patient's personality and beliefs must sway the doctor in his decision as to when, if at all, the patient is to be told that the last stage has been reached, and how to tell him. Often the priest can and should tell him. We all know how peaceful death can be when it is faced without fear,

and equally how delicately the process of dying must be handled by all concerned so that nothing is allowed to ruffle the calm or break the stillness. William Hunter said 'How easy and pleasant a thing it is to die'—and this is true.

Death is not a hopeless thing; nor are the dying without hope. Therefore, if for no other reasons, our care of these patients is infinitely worth while.

Dr. C. J. Gavey (*Westminster Hospital*).—Laymen are gradually acquiring a knowledge of survival rates instead of death rates and it is proper that it should be so, for anyone who is stricken with a killing disease will tend to think of the possibility of recovery rather than the inevitability of death and so from the start a valuable defence is set up. Initial fears from increased knowledge are giving way to the feeling that something substantial can be done. The patient, now better informed, plays an increasing part in the management of his disease but at the same time our responsibility becomes infinitely more exacting.

Certain religious considerations are relevant to our work as doctors. When the situation seems hopeless, nothing remains to solace except Faith, but Faith can be like a . . . 'promontory of the sea, against which, though the waves beat continually, yet both itself stands and about it are those swelling waves stilled and quieted' (Marcus Aurelius). Most patients are not afraid of death but are reluctant to die. My view is that the doctor is not expected to minister himself but he is expected to see that spiritual help is available and to cooperate readily with the priest. Although there is a growing mutual respect, it is still common for the clergy to be reluctant to approach the doctor, and the doctor, the clergy. Then the help of an intermediate person, the Sister in hospital, or a friend or relative in general practice, is appropriate and welcome to all parties. It is very doubtful whether anyone should be allowed to die of chronic disease without some warning of that possibility, at least at the very end. In regard to the patient who is actually dying, I believe he is more often aware of the ministrations at the last, than the doctor might think on medical grounds. A doctor is recognized as one who is unbiased as to race or creed, which is perhaps the reason for the common unjust accusation that doctors are lukewarm in matters spiritual.

TELLING THE PATIENT

In the doctor-patient relationship, based on the Hippocratic Oath, the patient has implicitly charged the doctor to give him the maximum help in combating the disease and, as we doctors see it, the patient has in his own interest implicitly left this problem of telling to the doctor's judgment. It is a human right to know the truth about oneself, if the truth be known, and most doctors say that for themselves they would wish to know the truth: e.g. Osler, Cushing and others. The slightest doubt regarding diagnosis and prognosis will indicate the postponement, if possible, of intimation of the state of affairs until time has clarified the position medically, and prepared

the patient for bad news. All of us could quote examples of mistaken prognoses, but if only we remain aware of our fallibility we are not likely to do harm in this connexion, especially if we include what we don't know, when telling our patients. More patients would seek the truth if they realized that terminal illness is not as a rule attended by acute suffering; more would ask if they had the opportunity, hence the importance of regular visiting. Some do not want to know the pathology at work—simply their expectation of life. Others only want the sympathetic ear of a responsible person. It is not infrequent for the relative to ask that the patient be not told. This may be reasonable but our prime duty is to the patient. There is the occasional patient, rare in my experience, whom one feels should not be told lest the truth harries him and his family. Self-deception is sometimes fostered and it might be unwise to intrude at that moment unless some important family or public interest demands attention to his affairs. There is something to be said for the method of telling whereby a relative or close friend takes that responsibility, for, as Munk (1887) said, 'they do so without destroying his hopes, for the patient will still believe that he has an appeal to his physician beyond their fears'.

Perhaps half the population still believe that we usually avoid the truth. A few venerable physicians and surgeons have told no-one of a fatal issue if they could possibly avoid it. I have told many and never regretted it, but I have tempered the truth with such solace as I could muster, never closing the door until the very end, for, as Ogilvie (1957) has said, optimism is the greatest analgesic and hope is the most certain tranquillizer. Treatment is facilitated if the patient knows the rationale of it but once the position has been stated there is no place for reiteration. I have known some who, having known the truth, did not finally accept it and they thus found strength to go through their treatment. Mystery, fear of the unknown, may sap the patient's strength and undermine his morale. I have not met an example of suicide in a patient whom I have told, but I know it does occur very rarely.

TWO ATTITUDES

The fact remains that there are still two attitudes to be found amongst us. Those who tend to tell and those who tend not to tell. I feel that the tide is turning in favour of telling, and that is the line I take with students whose task will be greater than ours.

In conclusion, may I quote from the old physician, Dr. Farrier (quoted by Munk, 1887): 'The physician will not torment his patient with unavailing attempts to stimulate the dissolving system, from the idle vanity of prolonging the flutter of the pulse for a few more vibrations; if he cannot alleviate his situation, he will protect his patient against every suffering which has not been attached to it by nature'.

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THE HEALTH OF STATESMEN AND AFFAIRS OF NATIONS

By H. J. C. J. L'ETANG, B.M., D.I.H.

In the autumn of 1955, President Eisenhower had a myocardial infarction, in 1956 an intestinal obstruction said to be due to regional ileitis, and in November 1957 a cerebral vascular accident. In January 1957, Sir Anthony Eden, the British Prime Minister, who had undergone several operations on the biliary tract in 1953, resigned because of ill health. The resultant publicity was condemned by many unthinking people as an unwarranted intrusion into the sick room, and a sign of morbid curiosity and contemporary ill manners. It did, however, serve to remind the public that, whilst the modern statesman needs a high standard of mental and physical fitness, he is liable to suffer from the same diseases as others in the same age-group.

This lack of publicity in the past has resulted in the public being unaware that statesmen have continued in office when seriously incapacitated. Indeed, a survey of the medical histories of leading American and British statesmen in the past forty years reveals some most interesting clinical problems. The idea that a statesman's health can influence the fate of nations is not new. Between the two World Wars, MacLaurin,[1, 2] Giekie-Cobb[3] and Kemble[4] published books in which they described the physical and mental disabilities of certain historic figures and tried to demonstrate how these changes influenced world events.

WOODROW WILSON

The most complete study of this kind was made by Harley Williams[5] who tried to assess the influence that the ill health of Woodrow Wilson, the American President from 1912 to 1920, had on international affairs. Wilson had a cerebro-vascular lesion as early as 1906 when President of Princeton. By 1918, there was evidence of generalized arteriosclerosis and hypertension, and in his early dealings with Lloyd George, Clemenceau, and Orlando in Europe, and with the republican senators at home, he exhibited poor judgment, inflexibility of mind, and at times a dour obstinacy. After the left-sided hemiplegia which developed on October 2, 1919, his actions destroyed any hope of the American Senate ratifying the peace treaty and agreeing to enter the League of Nations. These measures were finally defeated in the Senate on March 19, 1920.

After Wilson's hemiplegia, the United States were virtually without a President, for any measures requiring his inspection or assent were first examined by his wife and personal staff! On April 13, 1920, he was able to hold a Cabinet meeting and Secretary Houston describes his condition as follows[6]:—

'He looked old, worn and haggard . . . he would not, or could not, take the

initiative. One member brought up the railroad situation, and Wilson seemed to have difficulty in keeping his mind fixed on it'.

His intellect impaired, Woodrow Wilson struggled on until early in 1921, when Warren Harding succeeded him.

BONAR LAW

Shortly after these events, Andrew Bonar Law, a future British Prime Minister, had a serious illness[7]. He was forced to resign the offices of Lord Privy Seal and Leader of the House of Commons on March 17, 1921, because of hypertension. After a period of complete rest his health seemed better, and on October 24, 1922, he became Prime Minister. In the following month there was a General Election, and during it, it was noticed that he appeared to be suffering from throat trouble which caused difficulty in speaking. These symptoms persisted and, although in April 1923 he attended debates in the House of Commons, he was unable to speak. In May, carcinoma of the larynx was diagnosed, and he immediately resigned. He died in the following October.

ROOSEVELT

The attack of poliomyelitis suffered by Franklin D. Roosevelt in 1921, which paralysed his legs, tended to obscure the other ailments which he had during his years as President from 1932 until 1945. As early as 1937, there was talk that he was suffering from a cardiac disorder[8]. His physician, Admiral Ross T. McIntyre, always denied this, although he would not allow him to fly above 7,500 feet when he attended the Casablanca, Cairo, and Teheran conferences in 1943[9, 10].

In 1944, before he started the campaign for his fourth term as President, there was further speculation about his health, not without reason, if the comments of his intimate associates are to be believed. Frances Perkins, his Secretary of Labour, for instance, describes the President at the last Cabinet meeting before the inauguration of 1945 thus[11]:—

'When he came in I thought he looked bad. . . . His clothes looked much too big for him. His face looked thin, his colour was grey, and his eyes were dull'.

The Cabinet was about two hours in session and this is how she describes his condition at its end:—

'The change in his appearance was marked. As I sat down beside him, I had a sense of his enormous fatigue. He had the pallor, the deep grey colour of a man who has been long ill. He supported his head with his hand as though it were too much to hold it up. His lips were blue. His hand shook'.

Shortly after this, he sailed for the Conference that was convened at Yalta in February 1945. On the voyage, Byrnes, then Director of War Mobilization and Reconversion, said of him[12]:—

'I was disturbed by his appearance . . . I feared his illness was not due entirely to a cold'.

It has been said that the concessions made to the Russians at Yalta were the mistakes of a dying man, whilst his supporters say he made a supreme effort

and was in full command of his faculties—very difficult surely to believe. It is true that Frances Perkins said his appearance had improved considerably on his return from Yalta, but his former Secretary of State, Cordell Hull, formed a different impression[8,13]:—

'He was general and vague. Now and then he lost the thread of the conversation'.

It was revealed early in 1957 that some of the pictures taken of Roosevelt at Yalta were suppressed, because his appearance was so haggard. It certainly seems that, however fit—or unfit—he was to go to Yalta, he was certainly not fit enough to contemplate a further four years in office, when he accepted the democratic nomination in 1944. He died of cerebral hæmorrhage in April 1945.

HOPKINS AND FORRESTAL

Handicapped as he was, it was natural that Roosevelt should nominate others to act for him at conferences, and to go on fact-finding missions. It is curious that his main agent was Harry L. Hopkins[10], a man so debilitated by illness that Roosevelt himself referred to him as a 'half man'. Hopkins, who was born in 1890, had most of his stomach removed on account of the presence of a carcinoma in 1937. Subsequently he had what would now be called the 'post-gastrectomy syndrome'. He lost thirty pounds (13.5 kg.) in weight and had steatorrhœa. His plasma proteins were low, and he had œdema of the ankles. He attended many conferences during the 1939-45 War, sometimes with Roosevelt, sometimes as his personal representative. Before, during, and after many of these meetings he collapsed, and had to be put to bed, and on some occasions at least, seems to have been quite unfit to participate in discussions affecting the lives of millions of people.

James Forrestal[14] became Secretary of the United States Navy in 1944, a position similar to that of First Lord of the Admiralty. In 1947, he became the first Secretary of Defence, and in the following year he had difficulties with the Secretaries of the three services on budget allocations. He suffered severe attacks in the Press and on the radio, and dealing with this period his biographer records:—

'As his fatigue increased some associates . . . felt that he became less and less willing to make decisions. Even after the decisions were made he frequently wanted to re-open them. . . . Indecisiveness increased the always heavy load of unfinished business . . . an accumulation that worried both Forrestal and his Staff, driving him to adopt a still more exhausting time table'.

He had intended to resign early in 1949, but President Truman advanced the date of his retirement. A severe mental depression followed, which seemed at first to respond to treatment. In May 1949, however, he fell to his death from the 16th floor of Bethesda Naval Hospital.

MACDONALD, BALDWIN AND CHAMBERLAIN

It is the fashion now to decry the political leaders of the nineteen-thirties, and to call them the 'guilty men' who failed to stop the dictators rising to power in Europe. There is good evidence that some of these leaders were sick men, rather than sinners.

J. Ramsay MacDonald was Premier from 1929 until 1935, and Lord Attlee describes his gradual decline in these words[15]:—

'His speeches became increasingly incoherent and for the last years of his life he was only a melancholy passenger in the Conservative ship'.

For a time he remained in Parliament, and Hugh Dalton, while describing a debate on the distressed areas in March 1936, says of him[16]:—

'It had long been clear to all, not only that his general health was bad, but that his mental powers were in decay'.

Stanley Baldwin held the Premiership from 1935 until 1937 and one can learn much about his health from the diaries and letters of an intimate friend which were later published[17]. The following extracts begin in 1936, the year Hitler re-occupied the Rhineland:—

February 21, 1936. Yesterday I breakfasted with the P.M. and found him rather sorry for himself. . . . There is nothing wrong beyond an inclination to get tired sooner than usual.

April 25, 1936. *Daily Mail* mentioned P.M.'s deafness as a contributory reason for resignation. I daresay in Cabinet with a large group around a big table it is a serious handicap.

July 7, 1936. He quotes Baldwin as saying 'I am too tired for any fresh effort. . . . How long do you want me to go on?'

July 24, 1936. Downing Street Secretaries are concerned about the state of Baldwin's health. It is impossible to get a decision about anything out of him.

September 18, 1936. I reported [to Lord Dawson of Penn] that the patient [Stanley Baldwin] was distinctly better, more alert and interested but showing little mental resilience, and already brooding apprehensively on coming burdens and responsibilities.

October 16, 1936. The P.M. is back at No. 10 very much rested. . . . There is nothing organically wrong with him. He lost his nerve and every burden became a nightmare. He will last till the Coronation we all hope, but if the foreign situation becomes very difficult he may break under it.

February 19, 1937. On Monday I had lunch with the P.M. . . . 'I shall sleep for a week when I get out of this' he groaned.

This was a Prime Minister who had to face the increasing threats of Hitler and Mussolini.

Neville Chamberlain, who succeeded Baldwin after the Coronation in 1937, and who incidentally had the family gout, at first conducted the nation's affairs with great confidence and vigour. All who remember the Munich crisis of 1938 must admire his fortitude, even if some will criticise his judgment. In December 1939, after three months of war, his biographer notices a change[18]:—

'Yet it is possible to detect a weariness, an added sensitiveness, a disposition to identify criticism with faction . . . some of this may have come from the physical machine slowing down, for the letters speak of much gout and minor ailments'.

The disastrous Norwegian Campaign in April 1940 was followed by what was for him an even more disastrous debate in the House of Commons which resulted in his resignation.

On June 16, 1940, his diary speaks of 'considerable pain'. An exploratory abdominal operation was performed on July 24, followed by a more extensive operation because of a neoplasm in the large bowel. For a time he remained in the Cabinet, but soon retired to the country to die in November 1940.

Is it not possible that the effects of the neoplasm were making themselves felt towards the end of 1939, and should not this fact be considered before cruelly criticising his conduct of affairs during that period called the 'phoney war'?

BEVIN, CRIPPS AND KEYNES

Next to the Premiership, the two most important offices in the British Cabinet are those of Foreign Secretary and Chancellor of the Exchequer. It is not generally appreciated that for a time after the 1939-45 War both the holders of these offices were invalids.

Ernest Bevin became Foreign Secretary in 1945 and, far from having merely to concern himself with the polite diplomatic exchanges of peace-time, found himself facing recurrent crises and threats of war. His own health was a continual cause of anxiety[19, 20]. As early as 1943 when he was Minister of Labour in the War Cabinet, he apparently suffered from angina pectoris and his health caused anxiety to his colleagues. In the spring of 1947 at the Moscow Conference he had a 'heart attack', so that his appearance at the next day's meeting was always doubtful. He was ill during the Colombo Conference and had to be carried in a specially built chair up the double flight of steps to the Council Chamber. Finally he was forced to spend each weekend in hospital. In March 1951 he reluctantly retired, and died of a final heart attack in the following month.

Stafford Cripps had never been a healthy man[21]. In 1914 he was rejected by the Army, and after being Deputy Superintendent of a munitions factory resigned in 1916 because of ill health which persisted until 1918. He was liable to gastric disorders the cause of which was not apparent, as well as to insomnia. In 1946, he collapsed during the Cabinet mission to India. In 1947, at a most crucial time in Britain's history, he became Chancellor of the Exchequer.

In June 1949 a serious financial crisis occurred owing to a growing dollar deficit, with its resultant increased pressure on sterling. Cripps spoke in the House of Commons on July 14, 1949, and his biographer says:—

> 'His speech on this occasion was as lucid as ever, but there was a weariness about it . . . he was not able to sleep, and suffering much from digestive trouble. He could not go on; he had forthwith to abandon the Treasury for six weeks of rest and recuperation in a Swiss Clinic'.

He returned to England on August 19, 1949, and the decision was taken by the Government almost at once to devalue the pound, a controversial decision for which some will always criticise him. His rest in Switzerland had temporarily brought improvement, but during the next six months, and as the debates in the House became increasingly long and bitter, his health deteriorated, and he resigned the Chancellorship in July 1950. Later in the year a spinal infection was diagnosed, and he was placed in a plaster cast. The infection did not respond to treatment and he died in April 1952.

Lord Keynes, the economist, has had an influence over world events in the past forty years which has exceeded that of many Chancellors of the

Exchequer, and many statesmen. He had a myocardial infarction in 1937, and had several recurrences. In 1945, after onerous Treasury duties in London and Washington, he attended the first meeting of the International Monetary Fund and Bank at Savannah, Georgia. Some observations by his biographer are of particular interest and significance[22]:—

'Some of those who were at Savannah detected in his passionate excitement about the issues at stake a symptom of physical sickness. It seemed contrary to his usual level of judgment to be so much exercised by matters which might be deemed of secondary importance. . . . This lack of physical fitness may indeed be the explanation of his emotional excitement at Savannah'.

Keynes had a further myocardial infarction while in the train returning from Savannah to Washington in March 1945, and died of a final attack in England the following year.

CONCLUSIONS

It is tempting to attribute failure of a statesman's policy to his ill health. Moreover, his defenders can use illness as an excuse, while his critics can say that a sick man should not have remained in office.

In the statesmen mentioned, it must naturally remain a matter of opinion how much their efficiency was affected by their various disabilities. That it was significantly affected, there is no doubt whatever.

In many occupational groups, work studies have demonstrated to what degree mental and physical changes may adversely affect performance. Statesmen seem to have been neglected, and here surely is a group to be investigated by the professional historian and the inquiring clinician.

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CURRENT THERAPEUTICS

CXXI.—ANTICONVULSANTS

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SINCE the most dramatic manifestation of epilepsy is the convulsion seen in the major attack, it is natural that drugs effective in any types of epileptic disorder tend to be grouped under the generic title of anticonvulsants. It is important to realize, however, that the term epilepsy is itself not at all satisfactory from the clinical point of view, and that it is much more logical to refer to the epilepsies, indicating that they are a group of disorders of varying characteristics, and possibly of varying origins.

THE CEREBRAL DYSRHYTHMIAS

Indeed, a title more scientifically justifiable is that of the cerebral dysrhythmias, for this implies that the disturbance is primarily due to an electrical disorder of cerebral activity, and the clinical and neurophysiological evidence available certainly indicates that these epileptic disorders are all forms of paroxysmal cerebral dysfunction accompanied by abnormal electrical patterns in the brain. The clinical evolution of our knowledge of these disorders has led us to certain forms of descriptive classification, themselves quite useful as diagnostic guides but sometimes a little confusing from the point of view of rational therapy.

It is also important to realize that all animals (including man) have a convulsive potentiality, and that given the necessary conditions a convulsion or some other form of dysrhythmic pattern may be produced in any being. In certain cases the onset of cerebral disease, inflammatory, vascular, neoplastic or traumatic in origin, fires off the abnormal rhythms and so produces that type of epilepsy which we usually call symptomatic and which, in addition to 'anticonvulsant' therapy, requires treatment (if any be available) for the underlying structural disease. This fact also applies to those alterations in the biochemistry of the body which may produce convulsive movements clinically identical with those of the epilepsies but usually known as epileptiform seizures. This is the type of attack seen in hypocalcæmia, in hypoglycæmia, or in uræmia. In these conditions the normal convulsive threshold is lowered by the changes in the biochemical media, and so a group of normal cells fires off dysrhythmically.

What follows from this therefore is that these dysrhythmic disorders may originate either in the abnormal electro-chemical activity of structurally normal cells, or from the activity of cells which are themselves structurally abnormal, either as a result of disease, of injury or of congenital influences, and that these structurally abnormal cells constitute the so-called seizure

focus. In applying anticonvulsants therefore we have to consider the twin possibilities that we may wish either to modify the biochemistry of the body or else in some way to modify the effects of abnormal discharges of abnormal brain cells.

MODE OF ACTION OF ANTICONVULSANTS

If these suggestions about the causation of convulsive attacks are correct, and on the present evidence it certainly seems that they are correct, anti-epileptic or anticonvulsant preparations may act in one of the following ways:—

(1) By countering these biochemical changes in the general cell population which may be responsible for the cerebral dysrhythmia.
(2) By producing biochemical changes in the brain cells themselves in such a way as to raise the general convulsive threshold.
(3) By direct effect upon pathologically altered neurones, thus reducing their tendency to set up abnormal discharges.
(4) By suppressing the transmission of discharges arising in these abnormal cells, thus preventing the spread to normal cerebral cells and the subsequent full-blown seizure pattern.

In discussing anticonvulsant drugs we are dealing primarily with those preparations which produce their effect upon cells which are structurally or functionally disordered within the brain, for, as already indicated, in clinical practice the term 'the epilepsies' (or cerebral dysrhythmias) is reserved for those seizures resulting from intra-cerebral abnormality, and not those due to the effects of more widespread biochemical disease. It is therefore with the drugs relating to these last three modes of action that we are concerned in this article. It will immediately be apparent that drugs of the potency required to bring about the suppression of convulsions are more than likely to have qualities undesirable and possibly harmful to the organism in general. Moreover, there is often an additional disadvantage that these anti-dysrhythmic powers are quite evanescent, whilst the undesirable side-effects prove to be both cumulative and prolonged. The situation has been further complicated by the fact that there has grown up the notion that all forms of cerebral dysrhythmia may be regarded as aspects of one and the same process, and that there is probably one epileptic entity with varying facets: a cerebral theme with numerous variations. There is, indeed, implicit in most pharmacological discussions on the subject the notion that there is a single ideal anticonvulsant drug which could be effective against all forms of dysrhythmic disorder and which is at the same time quite devoid of physical and psychological adverse effects.

Unfortunately it has to be recorded that, contrary to this theoretical concept, there is a body of pragmatic clinical knowledge to suggest that the dysrhythmias differ more widely in their origin than is sometimes thought, and that many different preparations may be required to counter the different dysrhythmic patterns. It is all the more important to realize from a practical point of view that so far it has not been possible to be absolutely dogmatic either about a causative or about a therapeutic differentiation of the various types of epilepsy. In practice the most effective drug in any of

the epilepsies is that drug which most nearly abolishes the attacks in a particular patient. The whole process of anticonvulsant medication in practice becomes empirical, and what suits a given patient with a given convulsive pattern may, in fact, not suit another patient with a seemingly identical disorder. In spite of this, certain guiding principles, based upon a combination of clinical and theoretical factors, are of value in deciding upon the programme of treatment in any given case.

SOME GUIDING PRINCIPLES

It seems probable that the differentiation of the dysrhythmias into three main divisions is justified, partly on grounds of response to therapy, and partly because the electrical abnormalities recorded in these types do tend to follow certain repeatable patterns:—

(1) Grand mal and Jacksonian or focal epilepsy.
(2) Petit mal, myoclonic jerks and akinetic attacks (the petit mal triad).
(3) Psychical (or psychomotor) epilepsy.

Before beginning therapy it is necessary to be clear in one's mind about the precise implication of each type of attack. Readers with a special interest in this matter are referred to 'Kinnier Wilson's Neurology' (Bruce, 1955), in which there is an excellent exposition of the descriptive classification of the epilepsies. It would be out of place here to discuss in detail the electroencephalographic abnormalities. For an account of the differing patterns to be found in the different types of epilepsy, the reader is referred to 'Recent Advances in Neurology' (Brain and Strauss, 1955). In passing it may be mentioned that the electrical abnormalities in type 1—the grand mal and Jacksonian epileptic attack—do seem to originate in cortical areas. In the petit mal triad, there is every reason to believe that the source of abnormality is much more deeply placed, whilst in the psychomotor form of epilepsy a definite electrical abnormality is commonly demonstrable in the temporal lobes, occasionally associated with structural changes in these areas. In other words, in certain instances there is a significant correlation between type of attack and type of electrical disturbance.

THE BROMIDES

The original use of bromides in the treatment of epilepsy appears to have arisen from the nineteenth century notion that certain types of epilepsy were in some way related to masturbation. Bromides had been reported as anaphrodisiacs, and the natural extension of this curious notion was to try them against epilepsy. This was done in 1857, and their immediate and subsequent success is well known. It was not until 1912, when phenobarbitone began to be used, that the bromides were supplanted as the major weapon in the management of the epileptic. They still have a definite value and in certain circumstances may achieve successful control when all else has failed. Unfortunately their indiscriminate use led to the development of many cases of intoxication and no doubt contributed very largely to the discrediting of

bromides when newer drugs became available. Their beneficial action is probably confined to cryptogenic epilepsy of the grand mal type, and they are useless in psychomotor and petit mal epilepsy. Indeed, if petit mal is associated with grand mal the control of the grand mal by the bromides may lead to a rather alarming outbreak of the petit mal type of attack.

The principal toxic manifestations are acneiform dermatitis, mental disturbances of all types, dysarthria, ataxia, tremors, and variable motor and reflex changes, simulating many forms of organic neurological disorder. It is important to have a periodic check of serum bromides whenever patients are being treated for long periods. In the presence of any symptoms of skin, mental or neural affection, a level of more than 9 milliequivalents per litre should be regarded with suspicion. The symptoms can be relieved almost immediately by stopping the drug and giving sodium chloride.

The dose usually required to control grand mal epilepsy ranges from 0.75 to 1 g. four times daily. They may be used in combination with other anticonvulsants for mixed types of epilepsy.

THE BARBITURATES

All the barbiturates given in anæsthetic doses can abolish convulsions, but only phenobarbitone, together with its close relative, mephobarbitone, possesses the specific anticonvulsant action in controlling seizures at dosage levels which do not interfere significantly with the normal function of the patient. Mephobarbitone has rarely been used and it is phenobarbitone which has achieved the greatest popularity since its introduction in 1912. The reasons for this popularity are easily seen, for, in addition to its cheapness, it has a wide spectrum of effectiveness, is of low toxicity, and requires no elaborate laboratory control for its safe usage. Its main value is against grand mal epilepsy but some success is often achieved, using it alone or in combination with other drugs, in the management of both psychomotor and petit mal attacks. The symptoms of overdosage are those of excessive drowsiness and these are usually easily countered by reducing the dose. More rarely, certain patients may develop skin rashes, and occasionally blood dyscrasias—particularly macrocytic anæmias—have been shown to develop. Although they have occasionally been incriminated as causing granulocytopenia, it seems that it is only when they are incorporated in mixtures, particularly those containing amidopyrine, that this complication may occur. In short, with the exception of what may occur in a very small number of specially sensitive patients who may develop skin or blood disturbances, the toxic effects of the barbiturates are attributable in the main to their misuse rather than to their use. One great advantage of phenobarbitone is that it can be used with safety in the treatment of children.

The dose in the adult ranges from ½ grain (30 mg.) three times daily, to 1½ grains (100 mg.) four times daily. For children the dose is adjusted according to size. In certain cases of nocturnal epilepsy it is usually suf-

ficient to administer 1 grain (60 mg.) of phenobarbitone shortly before retiring, as it is fairly rapidly effective and does not require a prolonged build-up.

THE HYDANTOINS
(PHENYTOIN SODIUM AND METHOIN)

The value of bromides and of phenobarbitone in the symptomatic treatment of epilepsy was discovered more or less by chance association and by deduction that their sedative properties might have an anticonvulsant effect. The later drugs (table I), beginning with the hydantoins, were evolved as

Drug	Dosage	Side-effects
Phenobarbitone	½ to 1 grain (0.03 to 0.06 g.) thrice daily	Skin rashes. Excessive drowsiness. Macrocytic anæmia (rare).
Phenytoin sodium ('epanutin'; 'eptoin')	¾ to 1½ grains (0.05 to 0.1 g.), up to three or four times daily	Gum hypertrophy. Macrocytic anæmia (rare). Skin rashes.
Primidone ('mysoline')	0.25 to 0.5 g., up to a total of 2 g. a day	Drowsiness, dizziness and ataxia. Macrocytic anæmia (rare).
Phensuximide ('milontin')	0.5 g., up to four times daily	
Troxidone and paramethadione ('tridione' and 'paradione')	0.1 to 0.3 g., up to four times daily	Glare. Sore throat. Skin rash. Blood dyscrasia. Renal dysfunction. Hepatic disorder.
Mesontoin ('methoin')	0.1 g., three to four times daily	Skin rashes (should not be given with troxidone and paramethadione). Blood dyscrasia.
Chlortetracycline ('aureomycin')	0.125 to 0.25 g., up to four times daily	Diarrhœa. Avitaminosis (always give vitamin supplements).
Acetazolamide ('diamox')	0.25 g., two to four times daily	Still under trial.
'Phenurone'	0.25 to 0.5 g., three to four times daily	Blood dyscrasia. Gastro-intestinal disorder. Hepatic disorder. Renal disorder.
Benzchlorpropamide ('hibicon')	0.25 to 0.5 g., four times daily	Dizziness. Tremor. Gastro-intestinal upset.
Bromides (sodium or potassium)	10 to 20 grains (0.6 to 1.3 g.), up to four times daily	Drowsiness. Confusion. Skin rashes.

TABLE I.—Anticonvulsant drugs: dosage and dangers.

a result of study of chemicals considered to have possible anticonvulsant effects. It was in this way that phenytoin sodium was discovered by Putnam and Merrit (1937). The principal value of the hydantoins lies in the fact that they are not sedative in their action, but exhibit, both in the experimental animal and in the epileptic patient, a definite ability to raise the convulsive threshold. They are valuable mainly in the treatment of grand mal and the so-called psychomotor attacks, but there is sometimes definite improvement when using a combination of phenobarbitone and phenytoin sodium in the treatment of petit mal. Like phenobarbitone, phenytoin sodium is characterized by a very low degree of toxicity, but methoin occasionally gives rise to troublesome leucopenia, and when patients are being treated with the latter drug it is always wise to have blood counts—in the first instance at daily intervals, later at weekly intervals and then once

monthly. Both phenytoin sodium and methoin will occasionally produce gingival hypertrophy, and in certain cases disorders of the skin, of the gastro-intestinal tract and of blood formation are encountered. On the whole, however, the drugs are relatively safe, though less safe than phenobarbitone.

The dosage recommended is 0.1 g. two to four times daily; the two drugs may be used in combination, or with phenobarbitone, in the treatment of grand mal. They can also be used quite safely with the drugs used in the treatment of petit mal epilepsy. 'Nirvanol' is another hydantoin, but this is now rarely used because of its serious side-effects, and in particular its effects upon the skin and on the blood.

THE DIONES (TROXIDONE AND PARAMETHADIONE)

Although originally synthesized, in 1944, as an analgesic, the anticonvulsant properties of troxidone were soon recognized, and Richards and Perlstein (1945) soon showed that it was highly specific in the treatment of the petit mal epilepsies. In the history of the treatment of the epilepsies the petit mal group has proved extremely resistant and, although as already mentioned, certain cases seemed to respond to a certain extent to phenobarbitone and phenytoin sodium, there was a large group of the petit mal type in which severe disablement resulted. As has been hinted earlier, the source of the electrical abnormality in the petit mal type of epilepsy is probably different from that seen in grand mal and psychomotor epilepsy. Unfortunately, we do not know the site of action of troxidone, otherwise this might well shed some light on the interesting theoretical implications of the differential effects of this drug on petit mal and the other drugs on the grand mal type of epilepsy. Our own experiences have been largely with the use of troxidone, but the theoretical evidence available suggests that paramethadione and troxidone are very similar in their action and also in their toxic effects. What follows relates largely to troxidone but applies equally to paramethadione.

It has been suggested that the specific electroencephalographic abnormality indicating the need for troxidone is the spike-and-wave phenomenon, but our own experience is that any petit mal, with or without the spike-and-wave, may respond extremely well to it. Indeed, its effect is at times brilliant and remarkable; it is therefore all the more regrettable that its potential toxicity makes it a rather difficult weapon to use. The dosage which we employ for the adult is 0.3 g. three to seven times daily; for children 0.1 g. to 0.3 g. three times daily; the variation does not necessarily depend upon age or weight and the dose is adjusted to individual clinical response.

The principal side-effects in order of increasing severity are:—

(1) Drowsiness, which is rarely troublesome, and is usually present only in the first few days of treatment.

(2) After two to three weeks, and usually when the dose has reached over 1 g. a day, certain patients complain of a 'glare phenomenon', so that objects in bright illumination appear to be covered with luminous snow. There appears to be no structural defect to go with this phenomenon, which can be

countered by wearing dark glasses and can often be relieved by a slight reduction in the dosage of the drug.

(3) Other relatively minor reactions which may be mentioned are: gastric distress, dizziness, lightheadedness, skin reactions, and sore throats.

(4) The less common, and more serious, disorders include skin rashes, nephrosis, hepatitis, and serious blood disorders including agranulocytosis, aplastic anæmia, and thrombocytopenic purpura. These are potentially fatal complications, and it is on their account that regular blood and urine examination is called for in any patient who is being treated with troxidone. For this reason, too, it is not wise to give the drug to patients who have hepatic or renal impairment or suffer from any form of blood dyscrasia. In certain cases exfoliative dermatitis may develop and in such cases troxidone should be abandoned.

THE SUCCINAMIDES (PHENSUXIMIDE)

The succinamide derivatives have been studied for anticonvulsant activity in animals since 1950. Phensuximide is the only one which has so far been tested in the treatment of epilepsy, and it is not yet fully established as a satisfactory anticonvulsant. Zimmerman, in 1951, wrote enthusiastically about its effect in the petit mal triad but other authorities have been rather more doubtful about its value. We ourselves have used it fairly extensively both alone and in combination with other drugs, particularly primidone, and it seems that there is a definite, though perhaps restricted, place for this preparation in the treatment of the psychomotor and petit mal types of epilepsy. Its great advantage lies in its extremely low toxicity, and so far we have not ourselves encountered any side-effects attributable to it. Millichap (1952) reported some transient renal damage, and other toxic signs which have been recorded are nausea, vomiting and skin rash. It seems probable, however, that these minor side-effects are not particularly troublesome, and are no indication for interrupting treatment. The dosage is 0.5 to 1 g. two to four times daily.

'PHENURONE'

This is mentioned in passing, for it belongs to a new class of anticonvulsant drugs, departing from the traditional barbiturate or hydantoin ring structures from which most of the other drugs were derived. 'Phenurone' was synthesized in 1948. It has been used against grand mal and petit mal epilepsy, and it seems probable that it is effective in many cases which are resistant to other forms of treatment. Unfortunately, its toxic effects outweigh the advantages to be obtained in treatment, for blood dyscrasia, liver damage, gastro-intestinal disorder and renal complications have been reported so often as to make it unwise to employ this particular drug in the routine treatment of epilepsy. In certain cases, however, in which grand mal or, more particularly, psychomotor or petit mal epilepsy, has failed to respond in any way to all other forms of treatment, there is probably a place

for the use of 'phenurone', provided adequate supervision is maintained and careful estimation of blood formation, liver and renal function carried out regularly. The dosage is 0.5 g. three times daily, which can be increased to 0.5 g. five times daily, if necessary.

PRIMIDONE

This is a close associate of phenobarbitone, which was first synthesized by Bogue and Carrington (1953). Its anticonvulsant and other properties were studied both in animals and in psychiatric patients undergoing electric shock therapy, and it was found that the drug is capable of elevating the threshold or modifying the pattern of chemically and electrically induced convulsions. Side-effects are more prominent than with phenobarbitone and include gastro-intestinal disorder, some drowsiness, dysarthria and ataxia, and occasionally some skin rash. Several cases of macrocytic anæmia have been reported, but so far no fatal complications seem to have occurred. It is particularly valuable in the treatment of grand mal and focal epileptic attacks, especially in the control of epilepsy in patients who have undergone brain operations for cerebral abscesses. It can be used in combination with phenytoin sodium or phensuximide or troxidone, but should not be used with phenobarbitone since the two together tend to produce excessive drowsiness. The usual dose is 0.25 g. two to four times daily, but it can be increased to as much as 0.5 g. four times daily without any serious side-effects. Its relatively low toxicity and high potency have already won it a prominent place in the routine treatment of epilepsy of the grand mal type (Handley and Stewart, 1952; Liversedge and Lyons, 1954).

ACETAZOLAMIDE

In the earlier discussion on the theoretical considerations underlying the use of the anticonvulsants, it was suggested that it might be possible to condition the biochemical background to neural activity in such a way as to alter the activity of, or electrical transmission from, seizure foci, and so raise the convulsive threshold. It was shown some years ago that the sulphonamides had a profound effect upon acid-base balance in the body, and that they were inhibitors of the enzyme, carbonic anhydrase, which is found throughout the tissues of the body, including the blood and the brain. Recently acetazolamide, having been employed first as a diuretic, has been tried in the treatment of epilepsy since it was felt that its biochemical action might result in an alteration of the pH of the blood towards the acid side and so raise the convulsive threshold. It will be remembered that the advocacy of the ketogenic diet also depended upon this notion that a disturbance of the acid-base balance towards the acid side might suppress epileptic tendencies. Bergstrom *et al.* (1952) and Lombroso, Davidson and Grossi-Bianchi (1956) reported good results with acetazolamide in dosages of 500 to 750 mg. daily. We ourselves have used up to 2 g. daily, with good effect and with no toxic manifestations to date.

Since carbonic anhydrase is so widely spread throughout the tissues of

the body it is natural to expect that its inhibitor might have a wide spectrum of activity and so indeed it has proved—at least for limited periods. Cases of grand mal, petit mal, and psychomotor epilepsy resistant to other forms of treatment do at times respond to acetazolamide used in a dosage of 0.25 to 0.5 g. three or four times daily. It can be employed alone or in conjunction with other anticonvulsant drugs. In certain cases we have found its efficacy to wane after a period of two to three months but, apart from drowsiness, no serious toxic effects have been noted.

CHLORTETRACYCLINE

Our own particular interest in this preparation arose some four years ago when a small boy, aged 2, was admitted to the hospital in petit mal status. Thinking that this disorder might theoretically be due to some form of encephalitis we embarked upon a course of treatment with chlortetracycline. Within forty-eight hours this reduced his attacks from one thousand a day to nil. After a period of six weeks the chlortetracycline (125 mg. twice daily) was discontinued. The petit mal recurred with its former frequency. Re-institution of the therapy once more resulted in the abolition of the attacks and treatment was accordingly continued and has been continued for the whole of the intervening period with considerable success. It was of particular interest that we later read of reports that the tetracyclines had been found effective by other workers (Stamps *et al.*, 1951). We have employed chlortetracycline successfully in other cases and prefer to use it with phensuximide. The dose of chlortetracycline is 125 to 250 mg. two to four times daily. Additional vitamins should be given as chlortetracycline tends to disturb normal vitamin absorption. The drug is of low toxicity but may produce diarrhœa or other gastro-intestinal disorder. Its main drawback at the moment is its relatively high cost.

BENZCHLORPROPAMIDE

This drug has been used in the treatment of epilepsy but is not yet of proven value. It seems to be ineffective against psychomotor and petit mal attacks but may be helpful in grand mal. The adult dosage is 1 to 2 g. four times daily. Although its side-effects include dizziness, tremors and gastro-intestinal disturbance, it seems to be of relatively low toxicity, but its limited use may be responsible for the absence of reported serious side-effects.

GLUTAMIC ACID

The main clinical interest in this substance has previously centred upon its efficacy or inefficacy in the treatment of certain forms of mental defect. It has, however, been studied as a potential anticonvulsant. Price *et al.* (1943) claimed good results in the treatment of psychomotor epilepsy and petit mal, but Goodman *et al.* (1946) showed that glutamic acid was ineffective against electrically and chemically induced convulsions. Other clinicians are doubtful about its therapeutic value in epilepsy. The recommended treatment is 4 to 8 g. daily in divided dosage and it seems to be devoid of toxic effects.

STATUS EPILEPTICUS

When a patient is admitted in status epilepticus the underlying disorder is usually grand mal, although in rare instances one finds young patients in what may virtually be called petit mal status. In such circumstances the immediate aim is to arrest the continuing dysrhythmia. In grand mal status paraldehyde has stood the test of time and can be given in a dose of 8 to 15 ml. by deep intramuscular injection. This may be repeated after four to six hours if required, should the attacks recur. We have found it to be effective in all cases of grand mal status which we have encountered and, provided care is taken about the injection (the injection should be deep and well away from nerve trunks), it is without danger. Once the status is under control the patient can then be treated by the routine anticonvulsants. Phenobarbitone sodium, in a dosage of 3 grains (0.2 g.) may also be used four-hourly for the control of status epilepticus, but on the whole we have not found this as efficient as paraldehyde. Other drugs which are employed are vinbarbitone ('delvinal'), 5 grains (0.3 g.), and lignocaine ('xylocaine'), 1 to 2 mg /kg. of body weight intravenously, but they have not yet stood the test of time. On the rare occasions when a patient arrives in petit mal status troxidone is probably the most suitable drug. It is usually employed in a 20 per cent. solution and may be given intravenously or intramuscularly. The dose called for is between 1 and 2 g., repeated as may be necessary. In rare cases general anæsthesia may be called for to arrest grand mal status.

CONCLUSION

It will have emerged from the foregoing discussion that there is still a great deal that we do not know about the production of convulsions and the *modus operandi* of the anticonvulsants. Certain scientific and theoretical concepts have been examined and the evidence at present available has been summarized with a view to providing as scientific as possible a background to the employment of anticonvulsant remedies. What is important is to remember that the correct approach to the use of the anticonvulsants lies in the design of a form of treatment which, so far as possible, will abolish the cerebral dysrhythmic effects without producing untoward side-effects. For this reason one tends to work out a practical programme of treatment hinging largely upon the safety, as well as the efficacy, of any given drug.

When a new patient is seen suffering from a cerebral dysrhythmia of cryptogenic origin (for it must be remembered that symptomatic epilepsy may require specific treatment for the cause of the symptoms) the programme of treatment which we employ is as follows:—

No matter what type of epilepsy is present we begin with the cheapest and most innocent of the anticonvulsants—phenobarbitone. It is important to have obtained as accurate as possible a record of the number of attacks which the patient has been suffering before treatment, and then to be sure that the effects of treatment are assessed against this initial untreated phase. If phenobarbitone is ineffective we usually add phenytoin sodium to it. If

there is still lack of control we tend to apply our knowledge about the different types of epilepsy. Resistant grand mal is then usually treated with primidone and later with methoin. Acetazolamide may then be used and at times a combination of any of these drugs, but it is not wise to combine phenobarbitone and primidone. If, on the other hand, the type of epilepsy belongs to the petit mal group we usually move from the initial phenobarbitone and phenytoin sodium to phensuximide and later to troxidone and paramethadione. Whenever these two latter drugs are used one must be very careful to obtain initial basic blood counts and to have frequent blood counts in the early phases of treatment. If these are not effective, or if there are very frequent petit mal attacks, chlortetracycline should be tried either alone or in combination with phensuximide. There is still a place for the bromides but on the whole we have tended to relegate these to special individual cases. It has not been our practice to use benzchlorpropamide, because of its doubtful efficacy and the very high dosage required, but it is possible that it may be effective in certain cases.

It will be seen from table 1 that the numerous side-effects of the different drugs must be considered carefully and it is advisable to draw up a special form including reference to all the potential toxic effects of each drug, which can be checked off at each visit. As soon as successful control is attained, the patient continues on the preparation or on the combination which has been arrived at by this system of trial and error, but we usually see patients receiving troxidone at three-monthly intervals even though control has been established and when no side-effects appear to be resulting.

Finally, in cases of symptomatic epilepsy due to cerebral tumour or to cerebral abscess it is important that after operation the rules of anticonvulsant remedies should be strictly obeyed. There is always a tendency to try to reduce the dosage employed in any case of epilepsy and even to abandon it as soon as possible. Our teaching is that it is better to err on the side of giving too prolonged a course of treatment than to stop too soon, and so precipitate a relapse.

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MINOR SURGICAL PROCEDURES

I.—LOCAL ANALGESIA FOR MINOR SURGERY

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Under the general heading, 'Minor Surgery', can be listed a number of surgical procedures suitable to be performed in the general practitioner's surgery and it is with these that we are concerned in this article.

Local analgesia for these procedures falls under two main headings: infiltration and nerve block.

Infiltration.—This term is applied to those relatively minor procedures rendering only the actual site of the operation analgesic: i.e. removal of a small sebaceous cyst from the scalp (fig. 1).

Nerve block.—This requires a more precise technique and needs a knowledge of the nerve supply to the part upon which the operation is to be performed: i.e. nerve block to a finger for removal of a nail or splinter (fig. 2).

DRUGS AND DOSES

Two solutions only are required: lignocaine ('xylocaine') solution in strengths of 1 per cent. and 2 per cent. This is a good, quick-acting analgesic, suitable for injection and having excellent surface (mucous membrane) effect as well. It is relatively safe in the strengths advocated and, although it is supplied already made up with adrenaline solution, it is safer to add the adrenaline as and when required. Ampoules of 1:1000 adrenaline are readily available. Lignocaine does not need to have any 'hyalase' added to it, as it already has a marked 'spread' action of its own and has the added advantage of not being a vasodilator.

To make up a solution of lignocaine 1 per cent. with adrenaline 1:200,000 (the recommended strength), add 0.1 ml. of 1:1000 adrenaline to 20 ml. of the lignocaine. It is advisable also to have available a water-soluble gel preparation of lignocaine for use on mucous membranes such as the urethra. This is readily available from the drug firms. The 2 per cent. solution is for use only in the eye.

The maximal dosage of the 1 per cent. solution is 50 ml., of the 2 per cent., 25 ml., and of the gel, 0.5 g. For infiltration purposes it is permissible to dilute the 1 per cent. solution down to 0.5 per cent. but the total dosage remains the same.

INSTRUMENTS

It is suggested that syringes and needles used for local analgesia be kept solely for that purpose; risk of infection is thus reduced. Two 10-ml.

syringes and two 2-ml. syringes are all that are necessary, together with some small intradermal needles, for raising a skin weal, and needles from 2.5 cm. to 7.5 cm. in length, of about size 16. The syringes should, if possible, be dry sterilized, having been carefully selected to withstand the heat of this procedure. If boiled, then they should be kept immersed in spirit and rinsed thoroughly before use. It must be emphasized that all injections must be carried out under the strictest aseptic precautions.

GENERAL PRINCIPLES OF INFILTRATION

Prepare and cleanse the skin as much as possible prior to infiltration. It is my considered opinion that all solutions used for skin preparation should be coloured distinctly, to obviate the risk of using the incorrect solution for injection. Raise a skin weal at the place selected for the first puncture, planning the injections to ensure that as few punctures as possible are made. Estimate the depth of any laceration or incision to be made and make the injection a little deeper. Select a needle long enough to insert the full length of the wound or incision; it may be necessary to make two injections on either side of the wound, as shown in fig. 3.

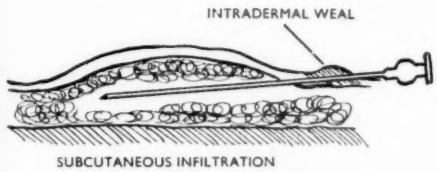

FIG. 1.—Infiltration analgesia.

Insert the needle through the skin weal, inject the solution as the needle advances; this has the effect of pushing any vessels out of the way. Use enough solution to give adequate effect; in fig. 3(a) about 15 to 20 ml. of the 0.5 per cent. solution and in fig. 3(b) 20 to 30 ml., would be average doses.

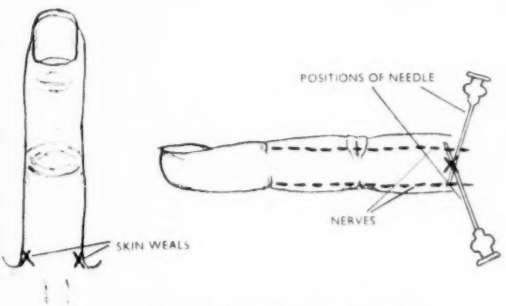

FIG. 2.—Nerve block. Finger (ring)block.

GENERAL PRINCIPLES OF NERVE BLOCK

Here the nerve supply to the affected part must be known, the injection being made at a point away from the site of operation. Having identified the position of the nerve or nerves supplying the area, the skin is cleansed, a weal raised, and the needle (the shortest possible is preferable) is inserted through the weal to the nerve. It is not necessary to elicit paræsthesia with lignocaine; it will be effective if placed near the nerve. For each nerve

about 5 ml. of the 1 per cent. solution, sometimes less, will suffice. Wait four to five minutes and then proceed.

THE SCALP

It is reasonably safe to assume that in this area of the body the general practitioner will be concerned mainly with lacerations and such procedures as removal of small sebaceous cysts. The technique here is infiltration. The analgesic solution is injected into the edges of the wound, making sure that an adequate margin, about 1 cm., is left for the insertion of the sutures. Shave the area first; then inject the solution, through a skin weal, about 1 cm. from the edge. It is better to use the adrenaline solution in the scalp as it has a tendency to bleed freely due to its excellent blood supply.

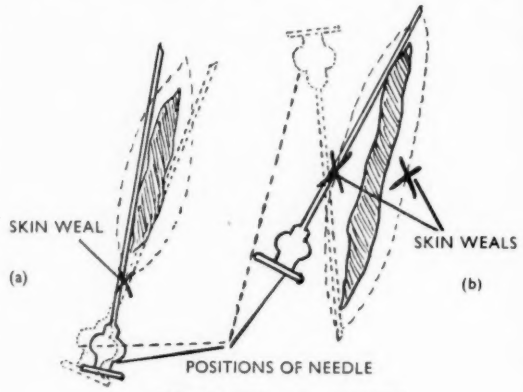

FIG. 3.—Infiltration of wound.

Sebaceous cysts are easily removed under local analgesia, the principle being to infiltrate carefully around the cyst and, as a final gesture, to inject a few millilitres directly under the cyst, thus raising it from the skull. Use the 1 per cent. solution with adrenaline (fig. 4).

THE EYE

Foreign bodies to be removed from the eye often require analgesia. Instil from 1 to 2 ml. of the 2 per cent. solution into the upper outer corner of the eye, leave for two to three minutes and good analgesia should result. Blepharospasm may be caused by the solution but this soon passes off. It is advisable to pad the eye after operation until the effect of the analgesia has worn off.

THE THROAT

It is not often that operations on the mouth or throat will be encountered, but sometimes a quinsy may have to be incised. The procedure is straightforward. Soak a swab, held in fine forceps or wound on to an orange stick, in the 1 per cent. solution of lignocaine and hold it against the area to be incised for three to four minutes. Adequate analgesia will follow.

THE UPPER EXTREMITY

As an emergency, it may be necessary to treat a fracture of the arm or some injury or infection of the hand or fingers.

A *fracture* may be reduced temporarily, before further treatment, by using a local analgesic. The most satisfactory method of doing this is to inject the hæmatoma at the site of injury directly with the analgesic agent. Raise a skin weal over the hæmatoma and, using a short needle, inject 10 to 20 ml. of the 1 per cent. solution into it (fig. 5). After a lapse of five to ten minutes it is surprising how much manipulation can be done with little or no pain to the patient. It is imperative that the strictest aseptic technique be observed in these cases. Infection can be serious.

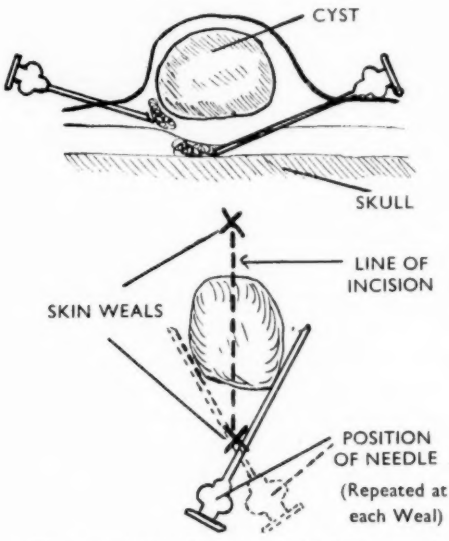

FIG. 4.—Injection for removal of sebaceous cyst.

The nerve supply to the *fingers* is via four nerves, two dorsal and two palmar, that run along the sides of the fingers from the metacarpo-phalangeal joint to the tip of the finger. It is by injecting these nerves that operations can be performed on the fingers. Raise two skin weals at the base of the finger, one on either side. A short needle is introduced into these weals and the 1 per cent. solution is injected, forming a 'ring' block of the finger. Only a small syringe and a small amount of analgesic must be used. The tissues must not be grossly distended. On no account must adrenaline be used here, as adrenaline and gross distension can cause ischæmia and necrosis. In septic conditions this block must only be used if the area of infection is distal to the first interphalangeal joint (see fig. 2).

THE THORAX AND ABDOMEN

Most conditions likely to be met with in this site are best dealt with by infiltration. Removal of various types of papilloma and the like can all be tackled by this method. A useful technique in the treatment of such painful conditions as the post-herpetic syndrome is intercostal block. The intercostal nerve runs along the groove in the lower border of the rib, deep to the external intercostal muscles, together with the artery and vein. First identify the nerve involved and then trace the rib back to its angle. Here it lies more superficially. Raise a skin weal in this position and, using a 5-cm. needle, insert it to hit the rib at its lower border. By gently moving the

needle it is possible to allow it to slip off the lower border of the rib and pass through the external intercostal muscle to lie in close proximity to the nerve. In this position hold the needle steady, attach the syringe and inject 10 ml. of 1 per cent. solution with the tip of the needle moving in and out slightly. Advance the needle only while injecting; this pushes the pleura ahead of the tip of the needle and prevents puncture (fig. 6).

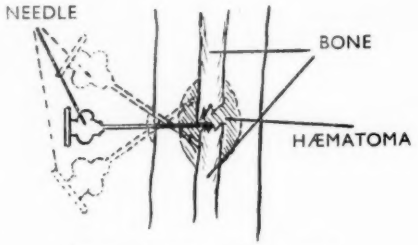

FIG. 5.—Injection of hæmatoma.

THE PERINEUM

In some patients it may prove impossible to perform a rectal or vaginal examination because of pain. A small quantity of the lignocaine gel smeared around the vaginal introitus or the anal margin will allow these examinations to be done without troubling the patient too much.

Painful hæmorrhoids can be dealt with similarly. Catheterizing a patient may be painful and here again the gel can be instilled into the urethra and massaged gently towards the bladder. Use about 6 to 8 ml. of the gel. Adequate analgesia is obtained in the majority of cases.

THE LOWER EXTREMITY

The remarks made about the upper limb apply equally in the lower limb. Toes can be dealt with as fingers.

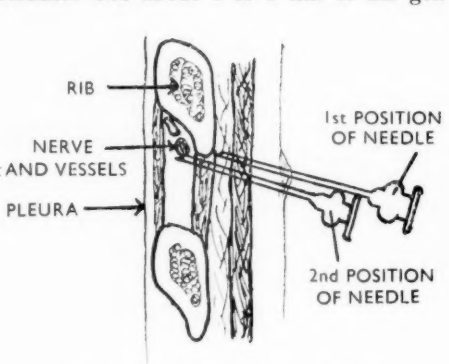

FIG. 6.—Injection of intercostal nerve.

SEPTIC CONDITIONS

In general, it is inadvisable to use injection or infiltration techniques in inflamed tissue: spread of infection and necrosis can easily follow. Abscesses, however, if ready for incision, can have a little local anæsthetic injected along the line of the incision, but nowhere else. Any other injection must be made well clear of any inflamed area. Carbuncles are particularly dangerous to deal with under local analgesia; spread can occur even in the most unlikely cases.

TOXIC EFFECTS OF LIGNOCAINE AND THEIR TREATMENT

All local analgesics can produce toxic effects, even in small doses, in susceptible people. These effects also occur with lignocaine. Dizziness, a

sensation of drunkenness, sleepiness, faintness even going as far as actual syncope, all occur with this drug. Normally they pass off with rest.

More severe reactions are sudden loss of consciousness, tremors and convulsions. Treat with rest, lying down, and possibly a vasopressor drug. If there are convulsions, the intravenous injection of a quick-acting barbiturate, such as thiopentone, in doses to control the convulsion, is advised. These conditions are rare but do occur.

REVISION CORNER

THE MANAGEMENT OF THE DRY SKIN

A DRY skin is a vulnerable skin and its owner is liable at any time to become a casualty because of this. Dry skin may be congenital or acquired, generalized or local, permanent or temporary, genetic or environmental in origin. It may sometimes follow nutritional deficiency or represent a cutaneous manifestation of a systemic disease such as myxœdema or lymphadenoma. The defect may reside in the epidermis itself, or the skin changes may result from morbid function elsewhere in the body, as is seen in the myxœdematous patient who lacks thyroid hormone. The influence of environment is shown by the well-known tendency for chapping of the skin to occur in frosty weather and an occupational cause of dry skin was recognized as long ago as 1700 by Ramazzini, who described 'chaps' in washerwomen.

Dryness is a manifestation of the ageing process in the skin. Little is known about the mechanism whereby the normal epidermis produces a healthy horny layer and we cannot influence the biochemical processes through which the epidermal cells elaborate that ingenious keratin-lipid-water complex, the horny squame. In recent years, however, several important advances have been made in our knowledge of the structure of keratin fibrils and the physicochemical properties of the horny layer itself. These have a considerable bearing on the problem of dry skin, and are worthy of some detailed consideration.

SOME BIOLOGICAL AND PHYSICAL CONSIDERATIONS

One of the first problems which animals had to contend with on leaving their aqueous environment to live permanently on dry land was that of desiccation. Different orders of animals dealt with this problem in different ways; and those who made the transition survived and flourished, as the penalty for failure was extinction. Some animals have been only partially successful in adapting themselves to terrestrial life, e.g. the moist-skinned animals, such as earthworms and amphibia, and they are considerably restricted in their

habitats. They have to dwell in swamps, on the margins of streams or moist soils, because their method of preventing desiccation, through the secretion of a moisture-retaining mucopolysaccharide on to the body surfaces, is relatively inefficient, and does not permit them to withstand low humidities. Reptiles, birds, mammals and most insects are able to live in drier habitats by virtue of their relatively impermeable outer covering. These vertebrates solved their desiccation problems largely with the help of the tough fibrous protein, keratin, whereas the insects and other terrestrial arthropods utilized the amino-sugar polymer, chitin, out of which they built their hard impermeable exoskeleton.

The amount of water vapour that air can hold increases with the temperature and it condenses to form dew when the temperature drops sufficiently. Evaporation is a dynamic process which may be said to occur when the number of water molecules leaving a surface in unit time is greater than the number of molecules entering it, and it depends more upon the energy at the surface than the humidity above that surface. This means that water evaporates most rapidly when the skin is warm and the relative humidity of the atmosphere is low. A movement of air over the surface will also influence the rate of evaporation.

SOME PHYSIO-CHEMICAL PROPERTIES OF THE HORNY LAYER

The human epidermis is an epithelium which produces a solid protective layer of dead 'cells' or squames on its surface—the horny layer. Indeed, the production of this layer is its principal function, and the survival of the underlying tissues and ultimately of the organism itself, may depend upon the integrity of this outer protective layer. The squames forming the horny layer are flattened elongated structures which are closely packed together. They interdigate with, and are superimposed on, each other so as to form a laminated structure serving as a compact barrier against irritant chemicals, microbes and other noxious agents.

Each horny squame is made up of an outer husk, consisting of fibrils of the tough fibrous protein, keratin, which surrounds an inner kernel of lipid materials. Because of its polar groups, keratin, like all other proteins, has the property of binding water. Water is attached to these groups by the hydrogen bonds which are formed by the attraction of two electro-negative atoms for a proton. The water-binding powers of the horny layer are familiar to all of us, because we must have noticed that the skin of our palms and soles becomes corrugated and thickened if we soak them for a short time in warm, soapy water. We must also have noticed that the water is soon lost to the air by evaporation, but it has only recently been discovered that the horny layer will lose water through evaporation in most environments.

Keratin fibrils (micelles) may be regarded as linear polymers in which relatively crystallized regions alternate with amorphous regions. The molecules in the crystal-

lite regions are regularly spread but those in the amorphous regions are randomly arranged and tend to be more widely separated. Because of the close spacing of the molecules in the crystallite regions, these regions are more or less impermeable to reagents including water, whereas water is absorbed with comparative ease in the amorphous regions (Marsden, 1953). Astbury (1933) showed that only a small amount of water penetrates the crystalline lattice of wool keratin and that most of it is absorbed in the amorphous regions. Speakman (1944) studied the wool-water isotherm and came to the conclusion that the initial absorption of water is associated with the hydrophilic side-chains of the keratin and that the water absorbed later is responsible for the great reduction in rigidity of the wool fibre as moisture is absorbed. That similar conditions obtain in the keratin fibrils in the human horny layer is suggested by the behaviour of a piece of dry callus before and after immersion in water. Dry callus will resist deformation by a weight of 300 grammes, whereas the same piece of callus will bend under a weight of 10 grammes after it has been immersed in water (Blank, 1952, Pillsbury, 1956).

The elastic properties of the keratin fibrils forming the horny squames are of the greatest importance in preserving the integrity of the horny layer, since its pliability and resilience depend upon them.

Keratin fibres are extremely elastic and a human hair can be stretched reversibly 50 to 70 per cent. in cold water, a property which is made use of in the measurement of the humidity of the atmosphere by means of the hair hygrometer. When the horny layer dries out the keratin micelles lose some of their water of hydration and with it some of their elasticity. This loss of pliability renders the horny squames brittle so that the skin feels rough and becomes chapped. Blank (1952) showed that under most common environmental conditions the horny layer tends to dry out because more water is lost from the surface of the skin than can reach it by diffusion from below. The horny layer, however, does not dry beyond the limit of pliability (i.e., it retains its elastic properties) if the relative humidity does not drop below a critical level of 60 per cent.

It is because the relative humidity of the air is low in frosty weather and when there is rapid movement of the air, as in windy weather, that the horny layer dries out and chapped skin may develop, especially on exposed surfaces of the body.

The role of sweating in the prevention of desiccation has not been fully investigated yet, and Blank is inclined to discount it as a factor under most conditions. In this respect it is worth mentioning that absence of sweat glands does not always predispose to dry skin, in spite of statements to the contrary in the textbooks. I have under my care one such patient with congenital ectodermal dysplasia who shows no evidence of ichthyotic or xerodermatous changes in her skin. Blank's findings have been corroborated by Gaul and Underwood (1953).

SYSTEMIC THERAPY

It follows from all this that we can do little to help the dry-skinned patient by systemic means, unless we are dealing with a systemic malady or dietary deficiency, of which xeroderma is a manifestation. We can restore the normal texture of the skin and hair in myxœdema by giving thyroid extract, but there is no reason for giving thyroid to the euthyroid subject with a dry skin, however severe the disability. I have seen ichthyosis produced in a patient on a fat-free diet which cleared when she resumed her usual diet.

LOCAL TREATMENT

It has been said that the only way to treat a dry-skinned patient is to grease his skin, and broadly speaking this is true, but the proviso must now be added that his skin must be re-hydrated before grease is rubbed in. The reason for this is that grease serves as a water-retaining film and does not correct an alleged deficiency of fats in the horny layer; in fact, patients may find that grease rubbed into an already 'dry' skin may make it worse. It is important therefore to explain to the patient the nature of his disability and why he should apply the emollient after his skin has been moistened. Excessive exposure to soaps, alkalis, detergents and other degreasing agents should be avoided by dry-skinned subjects, and removal to a warm climate, when practicable, may benefit the more severely handicapped patient. No emollient can be said to have any advantage, other than cosmetic, over another in the management of dry skin. Each patient finds one which suits him best.

The milder degrees of dryness of the skin, particularly in *the aged*, are often helped by the addition of a teaspoonful or so of olive oil in their bath; the more severely affected will need to rub in the appropriate emollient after they have had their baths. Such patients should not linger too long in the bath and they should be sparing in their use of soap.

The *schoolgirl* whose hands get chapped in frosty weather should grease them well after washing, and must wear warm gloves if further desiccation by the cold winds is to be avoided. Dryness of the forehead and cheeks in younger children can be reduced by rubbing in the emollient before the child goes out of doors in cold or blustery weather. Central heating of the modern house is a factor in the production of dry skin, by creating a warm microclimate with a low humidity, and it may be necessary to ensure that water vapour is added to the air in the house. The *young housewife* with chapped hands is a candidate for early dermatitis unless she, too, follows the suggestions made for her schoolgirl sister.

Physical exercise, by producing sweating, is helpful in re-hydrating the dried-out horny layer and is to be encouraged whenever circumstances permit. Those whose work or recreation exposes them to the more severe effects of wind and weather should always wear protective creams or greases and in this respect the value of a good protective cream for ski-ing, mountaineering and sailing, which combines anti-desiccation properties with those of a good sun filter, cannot be over-stressed.

Chapping of the skin is unlikely in warm weather because there is a free flow of sebum at higher environmental temperatures, but it may occur when soap and water, detergents or other de-greasing agents are used to excess. Cracking and fissuring of the skin are liable to occur in hot desert climates, especially during sandstorms.

During the summer of 1957 I was asked for advice on this problem by the medical officer of one of the units in a British armoured division operating in the Libyan

desert in the hotter months of the year. He had found that the troops in his care suffered very badly from the drying effects of the desert winds and that sunburn was more frequent and more severe after exposure to such winds. There can be little doubt that the Bedouin Arab type of dress is best suited for such conditions, since the area of skin exposed to the risk of desiccation is minimal and the chances of maximal hydration of the horny layer are at their highest, because the microclimate produced under the *burnous* in these conditions ensures a high relative humidity. Contrast this with the British soldier in his shorts and shirt, exposed unprotected to the hot, dry macroclimate of the desert, with its rapidly moving air. It was suggested that the troops should wear as close an approximation to Bedouin garb as circumstances (and military tradition) would permit and that all exposed skin surfaces should be liberally anointed with an appropriate emollient possessing anti-sunburn properties as well.

In the event, grease paint provided by a film company which was 'on location' in the desert and more suitable modification of battle dress for sandstorm conditions (the C.O. drew the line at Arab head-dress!), substantially reduced the number of troops who become climatic casualties (Knight, 1957).

Finally, the most difficult problem of all, the management of the severe ichthyotic, should be dealt with along the lines already laid down and the practitioner may be surprised at the vast amounts of grease that these unfortunate people require to keep reasonably comfortable.

E. J. MOYNAHAN, F.R.C.P.
Assistant Physician, Dermatological Department, Guy's Hospital.

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NOTES AND QUERIES

Poliomyelitis Vaccine

QUERY.—Dr. Parish, referring to poliomyelitis in his article on 'Advances in Preventive Inoculation' (October 1957, p. 455), states that doctors who come in contact with acute cases may be immunized with poliomyelitis vaccine. Does this apply to G.P.s? Is the incidence of poliomyelitis among general practitioners higher than in the rest of the population, and is the vaccine useful for adults?

REPLY.—In a circular (16/57) to local authorities, dated November 19, 1957, the Ministry of Health states that poliomyelitis vaccine will be made available before next summer to certain additional groups, including general practitioners and ambulance staff and their families (i.e. people living in the same house).

With regard to the incidence of poliomyelitis, the statistical evidence adduced by Doll and Bradford Hill (*Brit. med. J.*, 1957, **i**, 372) suggests that doctors are specially at risk either of contracting the infection, or, having contracted it, of dying from it. Eight deaths from poliomyelitis were recorded in the five years 1951-56 among nearly 35,000 British doctors at risk, whereas at the rates of the general population only one death would have been expected to

occur. In an annotation on 'Doctors' Diseases' in the same journal (p. 394), the further suggestion is made that 'doctors may contract the disease no more often than laymen, but, because they keep working too long, pay the penalty of succumbing to a more severe attack'.

There is ample evidence that American (Salk) vaccine has conferred a high degree of protection on adults as well as on children.

H. J. PARISH, M.D., F.R.C.P.ED.

Greying of Hair

QUERY.—What is the recent theory on the premature greying of hair and what is the best preventive if there be any? If not, what is the best hair dye without any fear of dermatitis and other allergic manifestations?

REPLY.—Premature 'idiopathic' greying of the hair is an inherited abnormality in which the function of the hair melanoblasts is inherently weak and fails at an early age. It cannot be prevented. The determining mechanism is unknown, but there have been some interesting experimental findings, such as radiation-induced depigmentation of mouse hair and the inhibitory effect on this of cysteine hydrochloride.

For dyeing the hair, natural vegetable colours, such as henna, are innocuous, as, in the main, are metallic salts and compound dyes, but for various reasons none of these is satisfactory. By far the most effective hair dyes are the synthetic organic chemicals of the 'para' group. With these, however, there is an appreciable risk of allergic dermatitis, although its incidence, considering their widespread use, is much lower than was estimated at one time. A preliminary patch or 'touch' test should be done every time before the hair is dyed, but cannot be relied upon entirely and a negative result is not a guarantee that sensitivity is absent.

E. W. PROSSER THOMAS, M.D.

Treatment of Chronic Lupus Erythematosus

QUERY.—What is the treatment for chronic lupus erythematosus?

REPLY.—The majority of cases are improved by the use of anti-malarial drugs, mepacrine, chloroquine and 'plaquenil'. The effect is suppressive rather than curative, although permanent remissions may sometimes be accomplished. Chloroquine is to be preferred to mepacrine, as the occasional rare toxic complication has been reported more often with the latter drug.

The following is a suggested dosage scheme for chloroquine sulphate: 200 mg. twice daily for two to three weeks followed by 200 mg. daily for four to six weeks. Some improvement is usually evident after three weeks if the case is likely to benefit. The drug may have to be given continuously throughout the summer or courses of it may be sufficient to allay activity. Some cases seem to require 200 mg. thrice daily to bring the condition under control, but this large dosage is experimental and is not to be recommended at present. On this large dosage there may be interference with hair pigmentation, but this is a temporary effect. Chloroquine is slowly excreted and a watch should be kept for nervous restlessness, confusion, insomnia, headache, pruritus, nausea, diarrhœa and visual difficulties.

Treatment with chloroquine should be combined with measures such as screening the affected areas from the sun and the elimination of septic foci. Local treatment with CO_2 slush may be suitable for small patches of chronic discoid lupus erythematosus.

E. N. M. JOHNSTON, M.R.C.P.

Cerebral Arteriosclerosis

QUERY.—Four years ago a man aged 75 developed paresis of the right leg of gradual onset and is now found to have bilateral pyramidal lesions involving the arms and legs. Paralysis is not complete, the right limbs being more affected than the left. There is no wasting or fibrillation of muscles and there are no sensory changes. The cranial nerves and fundi oculi are normal. The only mental changes are of emotional instability, with a marked tendency to weep easily. He is occasionally incontinent of urine. There are no other systemic changes and the blood pressure is 150/100 mm. Hg.

The past personal and family histories are insignificant and he denies any venereal infection. The positive results of investigation are (a) osteoarthritic changes in the lower cervical spine, with marked reduction of disc space between C4 and C5: (b) Lange colloidal gold sol. test 4433322100 (in 1955) and 5322210000 (in 1947). The Wassermann and Kahn reactions of blood and cerebrospinal fluid are negative.

What is (a) the likely diagnosis in this case, and (b) what other causes are there for a paretic curve of this nature other than general paralysis of the insane and disseminated sclerosis?

REPLY.—(a) The total protein and globulin are not commented on, so I presume these constituents of the C.S.F. were normal. The emotional symptoms indicate that the localization of the lesion is cerebral rather than cervical, although the cervical spondylosis might well increase the signs of a pyramidal lesion.

The diagnosis would appear to lie between cerebral arteriosclerosis and general paralysis of the insane occurring at a late age, with negative serology. A treponema immobilization test might be helpful to exclude syphilis. I would favour a diagnosis of cerebral arteriosclerosis. The paretic Lange might indicate the presence of a small collection of encysted blood, possibly in the subdural space in the parasagittal region. (b) Cerebral hæmorrhage, subdural hæmatoma and certain forms of encephalitis such as subacute inclusion encephalitis and rarely in encephalitis lethargica.

HELEN DIMSDALE, M.D., F.R.C.P.

Calcium Oxalate Calculi

QUERY.—Would you please state the present position as to the origin of oxaluria and calcium oxalate stones and their prevention and treatment, if any.

REPLY.—Oxalate is normally excreted in the urine. Most of it is derived from oxalate-containing foods but some is endogenous. In certain persons the oxalates may abnormally precipitate in the urine to form gravel and calculi, the reason for this remaining obscure. Over-production of endogenous oxalic acid rather than a high intake of oxalate in the diet would appear to be the most likely cause. Derangement of substances which normally keep oxalate in solution is also a factor to be considered. The treatment recommended is avoidance of foods with a high oxalate content, adequate fluid and vitamin A and D intake, adequate milk intake, alkalis and a low carbohydrate and vitamin C intake.

Primary calcium oxalate calculi occur in individuals with an acid urine and an apparently normal urinary tract. The nucleus of the calculus generally consists of calcium phosphate. This nucleus may start as a plaque beneath the epithelium of the renal papilla (Randall type I lesion), its exposure to the supersaturated solution resulting in stone growth; or it may start by precipitation of salts from the urine in the efferent channels (Randall type II lesion).

Because of the calcium phosphate nucleus, acidification therapy is of value in preventing these calculi, although solubility of the calcium oxalate will be practically unchanged. A low urine output should be avoided even for transient periods. Operation is generally indicated if a stone has formed which is of a size unlikely to be passed spontaneously. If situated in a calyx, removal of the stone-containing calyx by the operation of partial nephrectomy is more likely to prevent a recurrence than is extraction of the stone through a nephrolithotomy incision. Eradication of any urinary infection, ingestion of large amounts of fluids and limitation of calcium and phosphorus intake should follow operation. Derivatives of salicylic acid have been recommended as an addition to this treatment, because these increase the output of glucuronosides in the urine, thereby augmenting the solubility of the stone-forming substances. The possibility of hyperparathyroidism in patients with calcium-containing stones, especially if recurrent, must also be investigated.

A. H. JACOBS, F.R.F.P.S.

Dienœstrol in Carcinoma of the Prostate

QUERY.—Mr. X is about 70 and his wife a few years younger. His symptoms suggest an enlarged prostate gland, though it seems to be normal on rectal examination. The question is whether he should be treated with dienœstrol until it can be decided whether he should have his prostate removed. The reasons for giving him dienœstrol would be (a) as a prophylactic against carcinoma pending diagnosis and operation; and (b) to relieve the symptoms, especially the nocturnal erections which wake the patient up. They are not only a nuisance; the patient's great fear is that if he went to hospital it might happen there. Thirty grains of potassium bromide at bedtime does not seem to have any effect. He is extremely happy with his wife but has not had any intercourse for some years. What are the risks of treatment with dienœstrol? The books refer to undesirable side-effects but do not say what they are. Would there be any risk that the man might lose his love for his wife? (I mean as a general rule.) Does it cause any alteration in the man's character, or any deterioration in mental ability or keenness? What, briefly, are the effects?

REPLY.—There is no evidence that dienœstrol is prophylactic against carcinoma of the prostate. Apart from nocturnal erections the symptoms in this case are not mentioned. As to the effect of dienœstrol on erections it is probable that the œstrogen would require to be given in rather high dosage to ensure that erections would not take place. The principal side-effects of œstrogen therapy in a man are impotence (and in this case, clearly, this is not an undesirable side-effect, but one of the chief objects of the treatment) and gynæcomastia with pigmentation of the nipples. The degree of gynæcomastia varies considerably depending upon the sensitivity of the breast tissue to œstrogen. Some elderly men are relatively resistant and show such minor changes that they may not be noticed, even by the patient himself, especially if he happens to be rather overweight and his

mammary region is already rather infiltrated with fat. There is no risk of his losing his love for his wife as the result of his taking dienœstrol, nor will it alter his character or cause deterioration in mental ability or keenness.

PETER BISHOP, D.M., F.R.C.P.

Fluorescent Lighting

QUERY.—I should be glad to know if you can let me have any literature against the use of fluorescent lighting. I have always found it extremely trying, and I believe it is not permitted in schools in France and I think elsewhere.

REPLY.—I do not know of any reputable evidence that any harm is caused by efficient fluorescent lighting. From time to time we have looked into this question, and in order to check on any recent work I consulted Mr. H. C. Weston, of the Institute of Ophthalmology. He, too, was not aware of any evidence against the use of fluorescent lighting as at present used. Indeed, he said that the evidence was rather the reverse and gave an instance of a school of partially sighted children in Birmingham where the introduction of fluorescent lighting had proved very advantageous. He also mentioned that in France the authorities had in the early days banned its use in schools, but had now adopted it wholeheartedly.

Dr. John Brown, who is a lecturer in my department, has looked up the literature and has come across one article entitled 'Cutaneous burns due to fluorescent lighting' by R. Ralph Bresler, *Journal of the American Medical Association*, August 27, 1949, p. 1334. This records a particular case in which laboratory workers worked for long periods while exposed to fluorescent lighting at a relatively short working distance. Some undesirable cutaneous reactions were reported but by shielding the fluorescent tube with a $\frac{1}{4}$-inch plate glass adequate protection was obtained.

You might be interested to refer to the book by H. C. Weston, 'Sight, Light and Efficiency' (H. K. Lewis & Co., 1949). The subject of misconceptions concerning fluorescent lighting is dealt with on pages 193 to 202.

PROFESSOR G. P. CROWDEN, O.B.E., T.D., M.SC., M.R.C.P.

Urethral Contraceptive

QUERY.—A patient of mine recently asked me about a new type of contraceptive for insertion into the penis. I personally have not heard of this before, and would welcome any information you could supply.

REPLY.—It is quite true that a rubber apparatus for insertion into the urethra has been designed, I believe in Japan, and that details of it have been sent to this country. If anything is calculated to produce urethritis and destroy the last element of pleasure in love-making it is this abomination.

KENNETH WALKER, F.R.C.S.

PRACTICAL NOTES

Diet in Steatorrhœa

THE value of a gluten-free diet in the management of idiopathic steatorrhœa in adults is demonstrated by a report by J. M. French and his colleagues (*Quarterly Journal of Medicine*, October 1957, **26**, 481). Of 22 patients with idiopathic steatorrhœa who were treated with a gluten-free diet, 16 recovered completely. All wheat and rye gluten was rigidly excluded from the diet. This meant that ordinary bread, pastries, cakes, biscuits, puddings, and gravies and soups thickened with wheat flour were banned. Special bread was made with wheat starch, whilst biscuits, cakes, pastries and the like were made to recipes using wheat starch, maize, or rice flour, cornflour (maize starch), soya bean meal with potato flour as a substitute. Confirmation that the recovery was due to the gluten-free diet was provided by the fact that five patients who had recovered and were then given gluten-containing food for a short period, immediately relapsed. Withdrawal of the gluten resulted in a return to normal health. Of the six patients who failed to respond to the gluten-free diet, five elected to revert to an ordinary diet. Four of these six patients have since died of complications of their illness and the remaining two are still in a state of ill health. It is stressed that the response to the gluten-free diet is sometimes slow and that it cannot be regarded as having failed unless a trial period of at least six months has been given. Once normal health has been regained, the gluten-free diet must be maintained indefinitely; otherwise relapse is almost inevitable.

Varicella Pneumonia

PRIMARY varicella pneumonia is not a rare disease in adults, according to S. Krugman and his colleagues (*New England Journal of Medicine*, October 31, 1957, **257**, 843). In support of their contention they report that 10 of the 30 adults admitted with varicella to the Bellevue Hospital Communicable Disease Unit during the first six

months of 1956 developed chickenpox pneumonia. The pneumonia became apparent between the second and fifth day after onset of the rash, and in all of them x-rays revealed 'generalized nodular densities', throughout both lung fields. 'The picture', it is said, 'was similar to that in sarcoidosis, carcinomatosis, and miliary tuberculosis'. The pneumonia was mild in three cases, moderate in three, and severe in four. 'Antimicrobial therapy did not alter the symptomatology or clinical course'. The respiratory distress usually subsided within one to three days. Two of the patients developed pleural effusion, and in one case this was massive. One patient died 'in pulmonary œdema' twenty-four hours after the onset of pneumonia. Necropsy revealed an extensive hæmorrhagic, predominantly mononuclear-cell pneumonitis, with 'histologic evidence of type A intra-nuclear inclusion bodies in the pulmonary exudate'.

Nitrofurantoin in Chronic Urinary Infection

THE protracted administration of nitrofurantoin to patients with ineradicable urinary-tract infection, particularly chronic pyelonephritis without demonstrable obstruction, may usefully complement the medical management of this difficult problem, according to E. Jawetz *et al.* (*Archives of Internal Medicine*, October 1957, **100,** 549). This conclusion is based upon their findings in 32 patients treated with nitrofurantoin: 13 for two to three weeks, 5 for four to nine weeks, and 8 for four to seventeen months. In the remaining six patients treatment had to be stopped because of the development of side-effects to the drug within the first two to five days of treatment. These side-effects included persistent nausea and vomiting, epigastric pain and maculopapular pruritic rashes. No other serious side-effects were encountered during the course of the investigation. The initial daily dose ranged from 300 to 600 mg. daily and in patients on long-term therapy this was reduced to 100 to 200 mg. daily. In the eight patients on long-term therapy, the urine culture became negative in all cases and remained so on maintenance therapy, except in one patient who developed hyper-infection with *Proteus mirabilis*. In all cases, however, bacteriological relapse occurred when nitrofurantoin was withdrawn. It is stated that 'in most instances the organisms recovered from the urine prior to nitrofurantoin treatment were so similar as to be considered identical with those isolated after months of treatment'. In every case the eight patients on long-term therapy were completely relieved of symptoms during the period of nitrofurantoin administration.

Post-partum Constipation

DIOCTYL sodium succinate is recommended by R. C. Schoenfeld (*American Journal of Obstetrics and Gynecology*, November 1957, **74,** 1114) as 'a valuable adjunct in the bowel management of the post-partum patient'. This is a surface-active compound which acts by lowering the surface tension in the gastro-intestinal tract. As it acts only as a stool softener, it was given in conjunction with 'alophen' which acted as a mild stimulant of gastro-intestinal motility. Patients were given a 50-mg. capsule of dioctyl sodium succinate as soon after delivery as they were able to tolerate fluids by mouth. Twelve hours later they were given one 'alophen' pill and another 50-mg. capsule of dioctyl sodium succinate. The latter was repeated twice daily for the next two days. Of the 203 parturient mothers given this treatment, only 13 (6%) complained of pain in the area of the episiotomies. An enema was given if there was no spontaneous bowel movement, but in 126 cases (62%) none was required. Previously, at least 90% of the mothers in this particular hospital had required an enema on the third post-partum day. It was also found that straining at stool was eliminated. No toxic reactions were encountered.

Trichomonal Vaginitis

SUCCESSFUL results are reported by H. C. Stewart *et al.* (*Lancet*, November 23, 1957, **ii,** 1028) from the use of a mixture of an antiseptic with local anæsthetics, known as 'locan', in the treatment of trichomonal vaginitis. The formula of the 'locan' pessary is:—

Amethocaine	¼ grain (10 mg.)
Amylocaine	⅛ grain (5 mg.)
Solution of benzalkonium chloride B.P.C.	¼ minim (0.02 ml.)
Lactic acid	½ grain (30 mg.)
Lactose	4 grains (250 mg.)

Patients were instructed to insert one pessary as high as possible in the vagina night and morning for six days. As controls, one group was prescribed two pessaries of acetarsol B.P.C. nightly for fourteen nights, and another was prescribed one 'penotrane' pessary (phenylmercuric dinaphthylmethane disulphonate) nightly for fourteen nights. The results showed that with 'locan' primary infestations were controlled in all cases, usually with one week's treatment; only 16% needed a second week's course. 'Occasional patients' needed up to four weeks' treatment, with increased dosage. The failure rate was 32% in the acetarsol series, and 34% in the 'penotrane' series. Reinfestations were controlled by 'locan' as readily as the first attack. Resistant strains were not found. It is stressed that 'no local treatment of the female alone can eradicate the disease from the community and prevent reinfestation'.

Palpable Livers and Spleens in Children

IN 317 apparently healthy infants and children, Brian McNicholl (*Archives of Disease in Childhood*, October 1957, **32,** 478) found the mean projection of the liver edge below the costal margin in the right midclavicular line to be slightly less than 2 cm. (range of 0.5 to 2.5 cm.) in the newborn infant, 1.6 cm. (0 to 3.5 cm.) in the remainder of the first year, 1 cm. (0 to 3.5 cm.) from 1½ to 10½ years, and 0.85 cm. (0 to 4 cm.) from 10½ to 16½ years. In infants the notches of the liver edge corresponding to the gall-bladder and the ligamentum teres were occasionally palpable. The spleen was palpated below the costal margin in 11.1% of the series: 13.5% of new-born infants, 7.2% of those from 1½ to 10½ years, and 16.6% of those from 10½ to 16½ years. The opinion is expressed that 'more success in feeling the spleen edge in infants will be achieved if its frequently axillary situation is remembered'.

Ulcers in the Mouth

THE suggestion that so-called 'peptic' ulcers in the mouth may be associated with the use of margarine for cooking is put forward by Harry Millett (*British Dental Journal*, November 5, 1957, **103,** 318). He reports two patients who 'suffered considerably' from such ulcers, both of whom were cured by giving up margarine and using only butter for cooking. An even more impressive case is that of a mother who had always used butter for eating and cooking up to the time her daughter was 8 years old. She then decided, on grounds of economy, to use margarine, and her child developed a number of peptic ulcers. These subsided when margarine was replaced by butter. Details are also given of another patient who was 'constantly affected with very painful peptic ulcers' until she engaged a new cook who would use nothing but butter for cooking. Her ulcers immediately healed and the only recurrence was when she had to stay in a hotel for a fortnight. On returning to home cooking the ulcers rapidly healed.

Bedside Valsalva Test

THE use of the Valsalva test (controlled forced expiration) as a means of detecting early cases of dyspnœa due to heart failure has proved of considerable value. R. W. Ard and R. H. Twining (*American Journal of the Medical Sciences*, October 1957, **234,** 403) have now described a simple method whereby the test can be carried out at the patient's bedside. The requisite equipment, which 'may be easily carried in every physician's bag', consists of an aneroid sphygmomanometer gauge attached to a short length of rubber tubing into which is fitted a mouthpiece, an ordinary blood pressure apparatus, and a stethoscope. The test is carried out with the patient resting in the supine position. The resting systolic blood pressure is recorded and the pressure in the cuff is then raised approximately 30 to 40 mm. Hg above this level. The patient is then told to expire quickly into the mouthpiece until he raises the manometer pointer to 40 mm. Hg and to hold it there for ten seconds and then to breathe normally. In the normal individual the blood pressure rises rapidly during the first one to three seconds of breath-holding, falls to practically the resting level by the end of ten seconds, and then rises, by 10 to 15 mm. a few seconds later. In patients with early congestive heart failure the blood pressure remains raised throughout the period of holding the breath, and there is no secondary rise after normal breathing is resumed. In a series of 60 patients on whom the test was carried out it was found to be 'positive' in 30, and in all but four of these other evidence of early congestive heart failure was found. In 26 the test was 'negative' and in none of these could any evidence of congestive failure be found. In the other four the result of the test was equivocal.

Warble-fly Infestation

A CASE of human infestation with the ox warble-fly (*Hypoderma lineatum*) is reported by J. M. McCloskey (*Journal of the Irish Medical Association*, October 1957, **41,** 121) from County Donegal, where infestation of cattle with the warble-fly is still common. The case was a boy aged 8 years who, in December 1956, complained of a painful swelling below the left mandible. Two weeks later he developed a painful swelling over the left eye. Still later a swelling appeared at the base of the skull and spread towards the right shoulder. Finally, in February 1957, a small lump appeared on the crown of the head, from which his mother expelled a grub. At the department of entomology, Queen's University, Belfast, this was identified as the penultimate larval stage of *Hypoderma lineatum*.

The mode of human infestation is similar to that of cattle. The adult lays one egg at a time and glues it to a hair. When the larva emerges it burrows into the skin through the hair follicle. A year is required for the full cycle of development and when the larva is ready to moult, it produces indurated swellings, usually on the upper part of the chest or back, or in the head or neck. The swelling becomes dome-like and an opening develops through which the larva may be expelled. The condition is twice as common in children as in adults, and males are three times as often infested as females.

REVIEWS OF BOOKS

The Chemistry of the Steroids. By W. KLYNE, D.Sc., PH.D. London: Methuen & Co. Ltd.; New York: John Wiley & Sons Inc., 1957. Pp. 216. Price 18*s.*

IT is a great test of the skill of a teacher to give a brief and intelligible account of a complex subject in such a way that it is of value to scientists working in other disciplines. This is Dr. Klyne's achievement and he has made available to the biological and medical worker the general nature of the present chemical knowledge of the steroids in which they may be interested. A large amount of information about the physical and chemical properties of these substances is usefully compressed into a small compass. Particularly valuable is the explanation of current thought on steroid configuration and steroid chemistry since this is of major importance in the grasping of the significance of so much of the other subject-matter. This includes a valuable section for reference on nomenclature, which is based on international agreement; it is particularly important that everything should be done to minimize the confusion which has arisen in this sphere of diverse practices.

The primary emphasis is placed upon the substances of biological interest but these are not restricted to the steroid hormones and include vitamin D, bile acids and cardiac glycosides amongst others. The reader should not open the book with any illusion that it can be quietly perused. Much concentrated attention will be required to grasp the significance of all the information given, particularly some of that on the schematic diagrams of synthetic and degradative pathways. Careful attention has been given to the bibliography which largely includes references of the widest nature. On the other hand there is an intriguing personal note in the citation of the origin of much of the work, the names of the leaders of the various 'schools' being given in the text; this also has the advantage of being able to avoid too many detailed references in the bibliography of a small book. Its value is aided by the presence of a meticulously prepared index.

Modern Trends in Neurology (Second Series). Edited by DENIS WILLIAMS, C.B.E., M.D., D.Sc., F.R.C.P. London: Butterworth & Co. (Publishers) Ltd., 1957. Pp. xi and 374. Figures 79. Price 72*s.* 6*d.*

A VOLUME of this nature cannot hope to be comprehensive and in making his selection the editor has made no attempt to continue the first series either in his invitation to contributors or in the subjects under review. He has expressed a bias towards the basic sciences so that the series differs from the first in containing less clinical description and as many as ten out of the twenty-four chapters are directly concerned with anatomy, physiology and pathology. Moreover, each contributor has been invited because of his special interest in the subject with which he deals and in this way one feels that in many of the essays one is being taken beyond the recent advance to the advancing fringe which more truly illustrates the modern trend. There is, in short, much here of interest and value not only to those who specialize in neurology in its broadest sense but to student and practitioner alike. The general level of contributions is high and the subjects are, for the most part, clearly presented. If one may be allowed a small criticism it is that a less agreeable modern trend also finds illustration and that is to pay insufficient attention to the style in which the essay is written. Although not all the contributors come from this country, 'polyarteric aneurysms' and 'investigational procedures', to quote but two examples, come from the pens of those who do. One of the contributors is also wrongly named and it is to be hoped that the commendable haste with which the volume appeared does not mean that literary has purposely been sacrificed to scientific worth.

The Physiology of Gastric Digestion. By A. H. JAMES, D.M., M.R.C.P. London: Edward Arnold Ltd., 1957. Pp. xi and 92. Figures 54. Price 28*s.*

A MONOGRAPH on gastric digestion, bearing the imprimatur of the Physiological Society, is certain of a welcome, and the author has attempted with considerable success a synthesis of the viewpoints and experiences of both physiologists and clinicians. It is, however, the duty of the reviewer to voice his comments. In the discussion on gastric acid secretion, the words 'free' and 'combined' acid still creep in. Dr. James is, of course, fully aware of their implications, but is there really any place for ideas which represent mid-Victorian concepts of acidity and whose retention can only confuse a further generation of students? The reviewer would have preferred a more hostile attitude to these outmoded terms. The discussion on the energetics of secretion would have been even more valuable had it emphasized the importance of blood flow. Shall we ever be able to analyse the effect of drugs on gastric secretion until we can distinguish their actions on secreting cells and blood flow separately? The classic paper by Cutting, Dodds and others is not even cited. To speak of the 'discovery of enterogastrone'

(p. 110) is surely premature. The claim, that an inhibitory extract can be prepared from the small intestine, has been very difficult to confirm. Even its confirmation would be a long way from satisfying the necessary criteria for the establishment of a hormone. Whatever the mode of secretion of acid, the simple, and, to the clinician, invaluable, concept that the output of acid is functionally related to the total secretory mass of parietal cells, merited fuller discussion. The most surprising omission, however, in any discussion on secretion is that of cortisone, which does not even appear in the index.

Such criticisms, which may simply reflect the reviewer's prejudices, should not deter the reader; the book can be recommended as a scholarly and critical introduction to its subject.

An Introduction to Functional Anatomy. By DAVID SINCLAIR, M.D. Oxford: Blackwell Scientific Publications, 1957. Pp. 426. Figures 166. Price 42*s*.

IN his foreword to this book Professor Sinclair writes 'It is impossible to understand the function of the body without an adequate knowledge of its structure, and, conversely, a good grounding in structure involves an appreciation of function. Of recent years the artificial barrier between the two subjects of anatomy and physiology has begun to break down: I have attempted to treat them as an integrated pattern of study'. Integration is the keynote of this work, and it is excellently done. The book is intended primarily for students of occupational therapy and physiotherapy, and therefore the nervous and locomotor systems are given particular attention. But it would be difficult to design a better survey of the human body as a first textbook for a medical student starting on the preclinical years.

The General Medical Council would do well to scrap the Goodenough report, with its rarefied academism, and get Professor Sinclair to design a syllabus for the preclinical studies.

Blood Pressure Sounds and their Meanings. By JOHN ERSKINE MALCOLM, M.B., CH.B., M.SC., F.R.C.S. London: William Heinemann Medical Books Ltd., 1957. Pp. vii and 93. Figures 45. Price 12*s*. 6*d*.

WING COMMANDER MALCOLM has attempted to seek a physical explanation of the Korotkov sounds based upon a new theory applied to the arterial system: namely, that of systemic arterial resonance. He claims that harmonic analysis of the brachial arterial pulse in man proves that not only is the arterial system in harmonic motion but that also the peripheral arteries, such as the brachial, radial and ulnar, are in a state of resonance. He also believes that arteriography shows that similar resonance occurs in the aorta and large arteries of the leg. In the latter part of the book he shows how this theory may explain certain aspects of arteriosclerosis and aneurysm formation, and may account for some of the radiological appearances found in arteries. This little book is a stimulating work but will need much confirmation.

Hypnosis in Health and Sickness. By GORDON AMBROSE, L.M.S.S.A., and GEORGE NEWBOLD, M.B., M.M.S.A., D.R.C.O.G., D.C.H. London: Staples Press Ltd., 1957. Pp. 196. Price 15*s*.

THIS book is written for the laity, who, stimulated by television, are getting an appetite for knowledge about mental processes, a modern variant of being interested in their souls. It is readable and tells of many facile cures and ameliorations wrought by suggestion under hypnotism; no failures are recorded. If read by many it will increase the medical hypnotist's practice considerably. To hypnotize is easy, but the value of the suggestions made under hypnotism will depend upon the wisdom and perspicacity of the hypnotist. Medicine is quite right in being suspicious of the therapeutic use of hypnotism: it means that for a time patients lose their critical sense which may or may not be to their advantage, and may have repercussions; it is for good or bad a temporary surrendering of personal independence of thought. Like some other psychiatric treatments it requires controlled trials by independent examiners if it is to become respectable. In man's long history the ability to be hypnotized by someone with superior knowledge or standing with its advantages of acting in unity, of being insensible to pain and fatigue, and of remembering orders, must have been a family-saving and tribe-saving force of the greatest value over many millennia, and those in whom the mechanism was best developed have survived. Probably the wise practitioner will, save in exceptional cases, be content with the powers of suggestibility that spring from his knowledge, his priestly office, his personality and sincerity.

Plaster-of-Paris Technique. By MARIAN ENGLISH, S.R.N., R.F.N. Edinburgh: E. & S. Livingstone Ltd., 1957. Pp. viii and 126. Illustrations 133. Price 15*s*.

MRS. ENGLISH is an expert at her craft and she has put herself to great trouble to pass on her knowledge to others by describing in detail every point concerned with the use of plaster of Paris. Technical skill is best acquired by example and practice, but this book is written with such simplicity and clarity that it makes precept almost equal to example—there remains only practice.

Plaster work is so essential a part of the orthopædic armamentarium that it might be thought that orthopædic surgeons were necessarily adepts, and this was the case some years ago. The concentration of injuries in fracture services, however, has necessitated the training of a new medical auxiliary, the plaster nurse or plaster technician. This is depriving house surgeons and registrars of much of the practical experience they would otherwise have gained, and it has led to a marked difference in quality between 'professional' and 'amateur' plaster casts. But surgeons have not been relieved of the obligation to become proficient in the technique and this book should be studied with care by every one of them who has to use plaster of Paris, as well as by medical auxiliaries specializing in this work.

Artificial Insemination in the Human. By A. SCHELLEN, M.D. Elsevier Publishing Co.; London: Cleaver-Hume Press Ltd., 1957. Pp. xii and 420. Price 72*s*.

DR. SCHELLEN has produced a most useful book on a highly specialized subject. Besides being a medical graduate he has been interested in medical sociology and has made a complete study of human artificial insemination. His book gives an excellent account of all aspects of the subject and not merely from a narrow angle, for the history, implications, and social and economic aspects are discussed as well as technique and the law as it applies to insemination in various countries. Any doctor or specialist who wishes to be able to discuss this subject with his patients rather than be prejudiced, can here find information clearly put. The author has had the advantage of studying the use of the method at various clinics in the United States. Of particular interest are the chapters on social and moral implications and the psychological motives of those seeking insemination. It is clear that the author, although giving both sides to the argument, is himself convinced that insemination from donated semen is unjustified.

Patients as People. By A. E. CLARK-KENNEDY, M.D., F.R.C.P. London: Faber & Faber Ltd., 1957. Pp. 251. Illustrated. Price 15*s*.

THIS is an excellent book. Dr. Clark-Kennedy takes a series of examples of the less common and more important aspects of disease as seen in the wards of a teaching hospital, and describes the personal story of a patient suffering from that disease. The examples are well chosen, and the stories are given with a human insight and knowledge of contemporary pathology and therapeutics, and a touch of kindly humour, that make them not merely readable but memorable. 'Patients as People' is to the student's textbook what a pre-registration house appointment is to the newly qualified but still unregistered doctor; indeed the book is the equivalent of a six months' appointment under a first-class clinician. It will help to effect that essential transformation that every student must undergo before he becomes a doctor: the transition from book learning to experience, from knowledge to wisdom, from the view that patients are cases to the understanding that they are people.

Medicine and The Navy. By J. J. KEEVIL. Vol. I 1200-1649. Edinburgh: E. & S. Livingstone Ltd., 1957. Pp. xii and 255. Illustrations 15. Price 40*s*.

IT is a curious anomaly that the country which is so proud of its Navy, and rates it as its Senior Service, should possess no authoritative history of its naval medical service. Surgeon Commander Keevil has now set out to rectify this omission, and in the first volume he covers the period from 1200 to 1649. The story he has to tell is a most depressing one. English sea-power may at times have reached a high level, but little, if anything, was ever done for the unfortunate sailor. Disease took a much heavier toll of life than enemy action, and the result of any naval action depended more upon the relative amount of illness in the opposing fleets, and the elements, than naval strategy. A naval medical service as such was non-existent, and even in applying what little was known about the prevention and treatment of disease we were far behind the Dutch and the Spaniards. Surgeon Commander Keevil lays much of the blame upon the internecine strife that prevailed at the time between the barber-surgeons and the physicians.

This is a book which will be studied with interest by all who have had any association with the Royal Naval Medical Service. It is fully and carefully documented, and whets the appetite for the succeeding volumes.

NEW EDITIONS

The Diagnosis and Treatment of Endocrine Disorders in Childhood and Adolescence, by Lawson Wilkins, M.D., in its second edition (Blackwell Scientific Publications, £6 12*s*. 6*d*.), needs no introduction to endocrinologists, for the author's own researches and the first edition of his book have gained him world-wide recognition. New chapters have been written on the chemistry and physiology of the thyroid and adrenocortical hormones, and descriptions have been given of the disorders which arise through an inborn error of the enzyme systems in these glands resulting in abnormalities of hormonal synthesis. The author fully describes his own original work on

the beneficial effect of cortisone on the adrenogenital syndrome. Further additions consist of the studies on sex chromatin patterns in hermaphroditism and gonadal dysgenesis and the advances in our knowledge of the metabolism of carbohydrates and of calcium and phosphorus. Each chapter on disorders of a particular gland is followed by an atlas of excellent photographs illustrating the conditions described. The subject-matter is concise, clear and to the point. The extensive bibliography consists of the most important and instructive papers on the subject. The author is to be congratulated upon his scholarly work.

A Textbook of Midwifery for Students and Practitioners, by R. W. Johnstone, C.B.E., M.D., F.R.C.S.ED., F.R.C.O.G., F.R.S.E., seventeenth edition, revised in collaboration with R. J. Kellar, M.B.E., M.B., F.R.C.S.ED., F.R.C.P.ED., F.R.C.O.G., F.R.S.E. (A. & C. Black Ltd., 35*s*.).—Three new editions of this textbook within the last five years testify to its enormous popularity. It is easy to appreciate why this is so for the book has an appeal of its own, the writing is easy to read, the arguments simple to understand, and the advice clear and concise. With so much to attract the student and the young practitioner it is disappointing so often to find the teaching of yesterday and the opinions of more than a decade ago. The breech hook, which is still illustrated and advised should long ago have found its rightful place in the museum. It is almost reluctantly admitted that Cæsarean section 'might possibly be considered' for brow presentation and is 'sometimes performed', but 'rarely necessary' for transverse lie, two conditions in which the operation has been increasingly used in an attempt to reduce fœtal mortality from obstetric trauma. The shadow of puerperal infection still falls across these pages, and it is still described as 'the greatest single cause of maternal mortality'. This unreasonable fear of sepsis alone can explain the statement that in some cases of disproportion 'craniotomy, even in a living child, may be safer for the mother than Cæsarean Section'.

It is true that in such new sections as have been written more modern views appear; antepartum hæmorrhage in both its forms, the placenta, renal failure, the rhesus factor, and so on, have been brought well into line with present-day ideas but they cannot hide the dust elsewhere. They do show, however, how admirable this book might be, and how very valuable to students and practitioners it could be were it in modern guise.

Medical Jurisprudence and Toxicology, by John Glaister, D.SC., M.D., F.R.F.P.S., F.R.S.E., in its tenth edition (E. & S. Livingstone Ltd., 47*s*. 6*d*.), has been so well brought up to date that it even includes the essential details of the Homicide Act, 1957. A commendable feature in these days of massive tomes is that the deletions exceed the additions, so that the new edition is actually some thirty pages shorter than its predecessor. In the preparation of this edition Professor Glaister has had the collaboration of Dr. Edgar Rentoul. As it has done since the turn of the century, this book provides the practitioner with an authoritative, concise guide to the practical aspects of a branch of medicine in which he is seldom involved but with which he must be conversant.

Biochemistry, by Abraham Cantarow, M.D., and Bernard Schepartz, PH.D., in its second edition (W. B. Saunders Company, 84*s*.), is an excellent book for medical students for whom it is essentially written. The book runs to around 800 pages and avoids the pitfalls of excessive brevity and the criticism of being too advanced for students. 'Pure chemistry' takes up about only one-third of the 29 chapters in the book, the remainder being written with direct clinical application, e.g. hormones, body glands, metabolism. In dealing with an extremely complex subject, the chapter on hormones is particularly well presented. The index is full and, from the student's point of view, an excellent feature is the many cross-references throughout the text. The bibliography on each chapter although not extensive is up to date. This textbook, combined at a later date in the curriculum with the companion book 'Clinical Biochemistry' of which Professor Cantarow is again co-author, should provide adequate material for those medical students who wish to make a more specialized study of this subject.

Einführung in die Augenheilkunde, by Prof. Dr. med. P. A. Jäensch, in its third edition (Georg Thieme, DM 27.50), gives a comprehensive view of all important diseases of the eye. The book is well illustrated and includes a useful appendix about industrial diseases of the eye, a brief explanation of the technical terms used and an official guide to compensation for injury or loss of eyesight. The combination of precise style and excellent illustrations as well as the moderate price make this introduction to ophthalmology eminently suitable for the clinical student and the general practitioner.

The contents of the February issue, which will contain a symposium on 'Coronary Disease', will be found on page A112 at the end of the advertisement section.

Notes and Preparations see page 149.
Fifty Years Ago see page 153.
Motoring Notes see page A95.
Travel Notes see page A99.

NOTES AND PREPARATIONS

NEW PREPARATIONS

'CANDAMIDE' tablets each contain 250 mg. of lithium carbonate and are indicated mainly in the hospital treatment of mania and hypomania, but 'can also be of use' in cases of mixed psychoses and in excited schizophrenics. Issued in bottles of 1000 tablets. (Camden Chemical Co. Ltd., 61 Gray's Inn Road, London, W.C.1.)

'CARBONET' dressings are made from an open-mesh gauze 'impregnated with a water-soluble polyethylene glycol mass', and are intended for use 'on all types of open wounds', providing 'a non-adherent barrier between the wound surface and overlying dressings'. They are sterilized ready for immediate use. Available in sealed tins containing either 36 dressings, size 3¾ inches (9.5 cm.) square (non-interleaved), or a 4-yard (3.7 metre) strip, 7½ inches (19 cm.) wide folded zig-zag. (Smith & Nephew Ltd., Bessemer Road, Welwyn Garden City, Herts.)

'FERSAMAL' tablets each contain 200 mg. of anhydrous ferrous fumarate (equivalent to 65 mg. of ferrous iron), and are intended for the prophylaxis and treatment of iron-deficiency anæmias. They are said to be 'exceptionally well tolerated', even by patients unable to tolerate other salts of iron. Available as uncoated tablets in tubes of 100 and bottles of 1000. (Glaxo Laboratories Ltd., Greenford, Middlesex.)

'GONADYL' tablets each contain 50 i.u. of serum gonadotrophin and are intended for the treatment of acne vulgaris. It is claimed that a high percentage of cases are 'either cured or greatly improved'. Issued in bottles of 25 tablets, for sublabial or sublingual administration. (Roussel Laboratories Ltd., 847 Harrow Road, London, N.W.10.)

'MYSTECLIN V' capsules each contain 250 mg. of tetracycline hydrochloride and 250,000 units of nystatin, with added sodium metaphosphate. Their range of anti-microbial activity is said to include 'gram-positive and gram-negative organisms, spirochætes, certain large viruses, certain rickettsias and *Endamœba histolytica*'. Available in bottles of 12 and 100 capsules. (E. R. Squibb & Sons, 17-18 Old Bond Street, London, W.1.)

'PROCTOSEDYL' is intended for the treatment of hæmorrhoidal conditions, and is available in the form of suppositories (boxes of 6) and as an ointment (5-mg. tubes). The content of each suppository and each gramme of ointment is: 5 mg. of hydrocortisone, 10 mg. of soframycin, 5 mg. of cinchocaine hydrochloride, and 10 mg. of æsculin. (Roussel Laboratories Ltd., 847 Harrow Road, London, N.W.10.)

'V-CIL-K' tablets each contain penicillin V potassium, which is said to give 'higher and faster blood levels than penicillin V acid'. Fasting levels have been shown to be 'higher than those obtained from the same dose of parenteral penicillin G'. Available in strengths of 125 mg. (200,000 units) and 250 mg. (400,000 units), in bottles of 12 and 100. (Eli Lilly & Co. Ltd., Basingstoke, Hants.)

ROYAL SOCIETY OF MEDICINE

THE next meeting of the Section of General Practice will be held at 8.15 p.m. on Wednesday, January 15, when the subject for discussion will be 'The Common Cold'. The opening speaker will be Dr. R. E. Hope Simpson, followed by Dr. A. T. Roden and Dr. J. Morrison Ritchie.

FORTHCOMING CONFERENCES

THE *Commonwealth Chest Conference* organized by the National Association for the Prevention of Tuberculosis, and incorporating the Annual Conference of the British Tuberculosis Association, will be held at the Royal Festival Hall, London, from July 1 to 4, 1958, inclusive. The conference will deal not only with tuberculosis but with other diseases of the chest and heart, and will include lectures, discussions and clinical meetings. Full details may be obtained from the Secretary-General, NAPT, Tavistock House North, London, W.C.1.

THE *Fourth International Goitre Conference* will be held at the Royal College of Surgeons, Lincolns Inn Fields, London, W.C.1, on July 6, 7 and 8, 1960. Full details may be obtained from Dr. Selwyn Taylor, 3 Roedean Crescent, London, S.W.15, or Dr. John C. McClintock, 149½ Washington Avenue, Albany 10, N.Y., U.S.A.

THE HARBEN LECTURES

THE Harben Lecturer for 1957 will be Professor A. Bradford Hill, C.B.E., Ph.D., D.Sc., F.R.S., whose subject will be 'The Experimental Approach in Preventive Medicine'. The lectures will be given on May 19, 20 and 21, 1958, at 5 p.m., in the Lecture Hall of the Royal Institute of Public Health and Hygiene, 28 Portland Place, London, W.1.

FILM NEWS

Reduction of Hæmorrhage during Surgery (35 and 16 mm., colour, sound; running time 30 minutes) describes the pharmacology of the

hypotensive drug, 'arfonad', demonstrates its site of action and gives examples of major surgical procedures in which its use is indicated. The film was made by the department of anæsthetics, Westminster Hospital, with the Royal Veterinary College, and produced by Derek Stewart. Available on free loan to medical audiences upon application to Roche Products Ltd., 15 Manchester Square, London, W.1.

THE WELLCOME TRUST

THE latest list of benefactions by the Wellcome Trust contains one which would have gladdened the heart of the distinguished philanthropist after whom the Trust is named. This is a grant of up to £26,000 to the Medical Research Council for the construction and shipment to Gambia of a twin-engined motor cruiser which will be used partly as a floating research laboratory, and partly to assist communication between the Council's Research Laboratories at Fajara and the field station near the village of Keneba, some 70 miles up the river.

MASS MINIATURE RADIOGRAPHY IN U.S.A. AND U.K.

BECAUSE of the possible hazards from x-ray irradiation, the U.S. Public Health Service has recommended the discontinuing of mass x-ray programmes for both schoolchildren and adults, and their replacement by skin testing for the detection of tuberculosis.

The Ministry of Health has issued a memorandum (H.M. (57) 94), 'deprecating' the 'uneconomical practice' of 'frequently repeated examinations of groups of an age, social class, or occupation in which there is no special risk of the development of pulmonary disease'. It recommends that mass miniature surveys of the same population should not be repeated more often than at three-yearly intervals. Further recommendations are that more static units for references from general practitioners and for others who specially need to be x-rayed should be developed and that 'it is of first importance that general practitioners should always be kept in touch with the results of examination of their patients, and that any lesion detected should be notified to the general practitioner concerned at the earliest possible moment'.

MISUSE OF STILBŒSTROL

THE council of the Pharmaceutical Society is 'deeply concerned about reported cases of the misuse by self-medication of stilbœstrol by persons who have not sought medical advice'. In a statement issued in 1955, the council advised pharmacists not to supply sex hormones or their preparations unless satisfied that the customer was obtaining them on medical advice, though not necessarily on prescription. From recent information received by the council, it would appear that misuse of stilbœstrol continues to occur, and the council again urge pharmacists not to supply stilbœstrol or any other sex hormone or their preparations unless they are satisfied that the purchaser is taking the drug under medical supervision.

MATERNAL MORTALITY

A 30 to 90% decrease in maternal mortality has taken place during the last twenty years, according to a recently published statistical report of the WHO covering 49 countries. The lowest maternal mortality rate is recorded in the United States (0.3 per 1000 live births for whites, and 0.5 for the population as a whole). In New Zealand it is 0.4, compared with 0.5 in Scotland, 0.7 in England and Wales, and 4.1 in Ceylon.

In the United States, 97% of deliveries among white women take place in clinics or hospitals, compared with 98% in Sweden, 70% in Scotland, 64% in England and Wales, 58% in Northern Ireland, and 22% in Italy.

MIDDLESEX MEDLEY

DEATHS from violence showed a sharp rise from 859 in 1955 to 1,014 in 1956, according to Dr. A. C. T. Perkins, medical officer of health for the county of Middlesex, in his report for 1956. The greater part of this increase was due to a 25% increase, from 397 to 483, in the number of deaths from accidents other than motor vehicle accidents. The latter increased by 10% to 250. There were 268 deaths from suicide, 13 of which were in the 15-24 years age-group.

The health control units at London Airport come under the ægis of the Middlesex county council. The number of ambulance cases dealt with here rose by 47 to 1,360, and the number of mental cases dealt with on arrival totalled 158, mostly British subjects. During the year four deaths occurred of passengers in flight: three were due to coronary thrombosis and one to 'hyperæmia of brain'.

Summonses under the Food and Drugs Act included one in respect of a can of beetroot found to contain a piece of rubber glove, one in respect of cakes wrongly described as 'rum baba' in that they contained no rum, and one in respect of buttered toast which was spread with a mixture composed largely of margarine.

SMALLPOX VACCINATION

IN 1956, eighteen countries were infected by smallpox by international travellers, and, as a result, eight of these countries had epidemics of disease, according to a WHO report. The countries in which epidemics occurred were: Ceylon, Ghana, Iran, Italy, Lebanon, Sierra

Leone, Sudan and the United Kingdom. The WHO committee on international quarantine has issued a warning against any relaxation of vaccination measures and has called for the use of potent vaccines as well as correct vaccination procedures.

U.S. DRUG SALES

A TABLE published recently in *The Chemist and Druggist* demonstrates the steady upward trend in the sale of drugs in the United States during recent years. A comparison of the net sales in 1953 and in 1956 shows the following increase (in million dollars): Abbott Laboratories 88.1 to 96.8; American Cyanamid 380.4 to 500.7; Parke, Davis & Co. 109.9 to 134.1; Pfizer 127 to 178.4; Smith Kline & French 52.9 to 104.6.

SCHIZOPHRENIA: A WORLD PROBLEM

SCHIZOPHRENIA now 'constitutes a major public health problem in many countries of the world where schizophrenic patients occupy nearly half the space in psychiatric hospitals', according to a WHO study group which met in Geneva recently. The report states that schizophrenics should be treated early with a minimum period of hospital care, and such early treatment requires early recognition of the disease, and 'thus more education of medical students and medical practitioners is needed, as well as education of the public'.

STUDENTS' STRIÆ

CUTANEOUS striæ (defined as 'skin markings, painless, sunken below the skin surface, at first red or purplish, later white') were found in 275 of the 862 students entering Leeds University in October 1956, according to Dr. S. E. Finlay, medical officer to the University, in a paper he read before the ninth conference on student health in British universities and medical schools, held by the British Student Health Officers' Association in Cardiff last year. This represents an incidence of 32% of university entrants. They were more common in women (56%) than in men (22%). The commonest sites were the lumbar region and the outer side of the thigh. In the majority of cases there was no history of weight gain or loss. It is therefore concluded that these striæ 'must be regarded as normal skin markings and not necessarily indicative of previous over-stretching of the skin or of endocrine abnormality'.

ELECTRICAL ANÆSTHESIA

THE Moscow Experimental Institute of Surgical Apparatus and Instruments claims to have invented a 'radio technical device for electrical anæsthetics'. In design it is said to resemble the machine recently produced by the Institute for the electrical induction of sleep. The new device has a double safety check: an electronic device for controlling the voltage, and an 'electro-mechanical arrangement which automatically switches off the current in case of emergency'. It is said that the new device may soon undergo clinical trials.

PUBLICATIONS

Current Medical Research is a reprint of articles published in the Report of the Medical Research Council for the Year 1955-56. Apart from two articles on developments in research policy, these are 'brief reviews of the more important findings of medical or biological research on certain selected subjects'. They provide an admirable guide for the practitioner to the major advances in medical research. (H.M. Stationery Office, price 2*s.* 6*d.*)

Advances in Tuberculosis Research. Vol. 8, *B.C.G.: A discussion of its Use and Application*, edited by Hans Birkhäuser and Hubert Bloch.—The contributors to this volume include a number of well-known names and come from seven different countries. About a third of the book is devoted to methods of preparation and application, and the remainder to the status and results of BCG immunization, with a final contrasting chapter on prophylactic chemotherapy. All but one of the contributors accept the value of BCG, but seem to vary in the degree of their acceptance; to the likely reader of this book this will be an advantage, for it will cause him to think. In this respect the one critical chapter, by Dr. J. Arthur Myers, unfair as it may be, is of great value. An interesting book. (Blackwell Scientific Publications, price 60*s.*)

Mathematics and Statistics for Use in Pharmacy, Biology and Chemistry, by L. Saunders and R. Fleming.—For the student whose mathematical education went no farther than the O level this book will be hard going but nonetheless he should be able to acquire an appreciation of the fundamental mathematical processes employed and with practice be able to use them. For the reader who had studied mathematics to a higher level and probably at a more leisurely pace, but for whom long disuse has blunted mathematical appreciation, this book is rather more than the 'brush-up' claimed by its authors. For these readers it must be a resounding success. (The Pharmaceutical Press, price 27*s.* 6*d.*)

Rehabilitation of the Elderly Invalid at Home, by G. F. Adams, M.D., M.R.C.P., F. M. McQuitty, M.B., D.OBST.R.C.O.G., and M. Y. Flint, M.C.S.P., is an account of a practical experiment in the

home treatment and rehabilitation of 85 disabled elderly invalids in Belfast. It is a valuable contribution to a problem of increasing concern to the community and will be read with interest and benefit by all general practitioners. (Nuffield Provincial Hospitals Trust, price 3*s*.)

How to Use a Medical Library, by Leslie T. Morton, A.L.A., in its third edition, has been brought right up to date and now includes a list of the principal abstracting journals, together with a brief description of some of the classification schemes to be found in medical libraries. With this little book as his guide, the practitioner who wishes to know how to make the best use of library facilities cannot go wrong. (William Heinemann Medical Books Ltd., price 7*s*. 6*d*.)

First Aid and Early Treatment of Burns in the Royal Air Force, by Group Captain G. H. Morley, O.B.E., F.R.C.S., is the second edition of Air Ministry Pamphlet No. 168, and has been written 'for service and civilian colleagues' who may 'suddenly be responsible for the conduct of cases of serious burns'. (H.M. Stationery Office, price 3*s*. 0*d*.)

Practical Notes on Nursing Procedures, by Jessie D. Britten, S.R.N., is a concise outline of nursing procedures. The opening chapter gives a good description of the organization and functions of a hospital, of the General Nursing Council and nursing associations. Subsequent chapters are devoted to routine work in the wards and special departments; the subject-matter is concise, carefully arranged to facilitate easy reference and simply but effectively illustrated. Miss Britten's book should have a wide appeal to student nurses in training. (E. & S. Livingstone Ltd., price 15*s*.)

Clean Air, by Sir Allen Daley, M.D., F.R.C.P., and others, is the latest booklet published by the *Family Doctor*. It provides the householder with a straightforward, authoritative account of how he can run his home comfortably and warmly without adding to the pollution of the atmosphere. It is briefly and admirably summed up in the sub-title: 'What you can do. What you must do'. It is only on sale to medical officers of health and local authorities. As it is available at the amazingly cheap price of 2*s*. a dozen, it is to be hoped that local authorities will take the opportunity of making full use of it in their campaign for instituting smokeless zones. (*Family Doctor*, B.M.A. House, Tavistock Square, London, W.C.1.)

A Clinical Bibliography of Gerontology and Geriatrics. Supplement One 1949-1955, by Nathan W. Shock, is a most useful compilation. Its mere size demonstrates the wellnigh gargantuan mass of articles, reports and other publications that are now being published on this subject. (Stanford University Press, price $15.00.)

OFFICIAL PUBLICATIONS

Report of the Ministry of Health for the year ended 31st December, 1956. Part I.—Between July 1952 and July 1956 the number of principals providing unrestricted medical services increased from 17,204 to 19,082—an increase of 10.5%. In the same period the number of single-handed practitioners fell by 12.6%, and the number of principals in partnership increased by 9%. In 1956, there were 333 partnerships of six doctors or more, compared with 241 in 1953. The age-structure of general practice shows little change, although there was a slight fall in the number of practitioners aged 35 and under. There were 1,263 practitioners aged 66 and over. Under the scheme for providing interest-free loans for building new premises, or converting existing ones, 239 applications have been received, but only 100 of these have been approved. One new health centre was opened during the year—in Sunderland—at a cost of £59,000.

An analysis of drugs dispensed by pharmacists for general practitioners shows that antibiotics were responsible for 6.8% of the prescriptions, but 20.6% of the net ingredient cost of prescriptions. Cough preparations were responsible for the largest proportion of prescriptions of any one group of drugs (12.4%), but for only 5.8% of the cost. They were closely followed by 'laxatives, purgatives, antacids etc.' (11.9% and 6.6% respectively).

The number of 'distinction awards' for consultants was: 269 'A' awards (£2,500 per annum), 673 'B' awards (£1,500 per annum), and 1,347 'C' awards (£500 per annum). (H.M. Stationery Office, price 11*s*.)

Report of the Committee to consider the future numbers of medical practitioners and the appropriate intake of medical students.—The committee, under the chairmanship of Sir Henry Willink, gives its reasons for reaching the conclusion that up to the present the medical schools in Great Britain have not been producing too many doctors, but that they will do in the next decade unless the intake of medical students is reduced by about a tenth. (H.M. Stationery Office, price 2*s*. 6*d*.)

Report on Resettlement of Disabled Persons during the year 1956 is a useful extract from the annual report of the Ministry of Labour and National Service for 1956. (H.M. Stationery Office.)

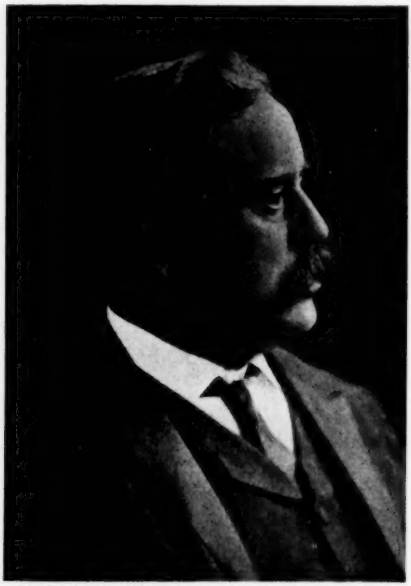
THE PRACTITIONER

Fifty Years Ago

'One should never put on one's best trousers to go out to battle for freedom and truth'.
—Ibsen: *An Enemy of the People*.

JANUARY 1908

'WE need not look for fresh reasons for wishing our readers a happy and prosperous New Year, or for novel phrases in which to express our wishes. There is a sense, of course, in which a good year for the medical profession means a bad year for the community at large; and cynical laymen are a little apt to picture doctors desiring epidemics in the spirit of the soldiers who used to drink to "a bloody war and quick promotion". It is superfluous to say (the Editor assures the reader) that our hopes for 1908 do not run upon those lines—that our desire is, above all



Sir Frederick Walker Mott, K.B.E., M.D., F.R.C.P., F.R.S. (1853-1926)

things, that the next twelve months may be twelve months of a steady progress in medical knowledge. Many difficult and important professional problems seem near to solution. . . . May some of them be solved and others advanced a stage before the year has run its course! Those are our aspirations, to which we may add our promise to help towards their fulfilment by continuing to present our readers with the results of the latest researches in a lucid and convenient form'.

'Notes by the Way' next offer 'reflections upon the virtue and value of winter holidays' at such places as St. Moritz, Davos, Le Pont, Grindelwald, and Adelboden ('Almost all of them can be reached in about eighteen hours from London'): 'The snow is certain to fall, and the sun is almost certain to shine at any one of them. A short stay in them, and a brisk participation in their amusements, has a bracing and invigorating effect, which no one fully realizes who has not tried the experiment'.

'An event naturally suggested by any mention of mountains is Dr. T. G. Longstaff's recent ascent of Trisul, in the Himalayas (23,406 feet). It is the highest of all undisputed ascents. . . . The achievement, at any rate, shows that mountain sickness is one of the complaints with which we are gradually learning to grapple. . . . We are hardly entitled to infer from Dr. Longstaff's success that the foot of man will some day tread the summit of Mount Everest. . . . Still we are entitled to take a hopeful view of the case'.

The *British Medical Journal* of September 1, 1956 (**ii,** 547-8) had a sprightly account by J. H. Baron of 'The Brown Dog of University College'. An editorial comment in *The Practitioner* fifty years ago reminds us that 'The "brown dog" incident at Battersea has brought a great deal of unmerited opprobrium upon the heads of the vivisectionists. It is certainly a principle of the law of England that, except in specified circumstances in which "reasonable force" may be used, no man is entitled to take the law into his own hands; but it does not follow that sympathy must always be refused to those who do. In the case of the attack on the monument of the "brown terrier dog done to death in the laboratories of University College", . . . the letter of the law was no doubt on the side of the monument. The "rags", however, remind us of a certain saying of Mr. Balfour's at the time when riots were apt to occur at pro-Boer meetings. There were, he said, "limits to the endurance of human nature" and, when these were strained too severely, excuses for riotous behaviour could be admitted. In the instance under our notice a breach of the peace was committed because a breach of the peace was provoked'.

The opening article, 'The Diagnosis of General Paralysis', from the pen of F. W. Mott, M.D., F.R.C.P., F.R.S., Physician to Charing Cross Hospital, and Pathologist to the London County Asylums, refers to Ford Robertson's recent claim to have discovered a diphtheroid organism, 'which he asserts is the cause of general paralysis, and he has named it Bacillus paralyticans'. Having taken his medical degree at University College, London, Mott became lecturer on physiology, and subsequently physician, at Charing Cross Hospital. The work on which his fame rests, such as the demonstration that general paralysis of the insane is a syphilitic infection, was done as pathologist to the L.C.C. Laboratory at Claybury (1895-1916) and later at the Maudsley.

J. M. H. Macleod, M.D., M.R.C.P., Assistant Physician for Diseases of the Skin, Charing Cross Hospital, takes as his subject 'Lupus Erythematosus: Observations on its Aetiology and Treatment'.

A symposium on 'The Urethra' is introduced by G. J. Jenkins, F.R.C.S., Lecturer on Applied Anatomy, King's College ('The Anatomy of the Urethra'); Arthur Edmunds, M.S., F.R.C.S., Surgeon to the Great Northern Central Hospital, describes 'The Causes and Varieties of Urethral Stricture'; Hugh Lett, F.R.C.S., Assistant Surgeon to the London Hospital, deals with 'The Treatment of Strictures by Bougie'; John Pardoe, F.R.C.S., of St. Peter's Hospital, discusses 'The Treatment of Acute Gonorrhœa'; and Charles Gibbs, F.R.C.S., Surgeon to London Lock Hospitals, writes on 'Gleet: Some Points in its Diagnosis and Treatment'.

Claude Ker, M.D., F.R.C.P., Lecturer on Infectious Diseases, Edinburgh University, presents 'A Review of Recent Work on Epidemic Cerebro-Spinal Meningitis': 'When we consider that the case mortality in Glasgow and Edinburgh has reached over 70 per cent., it is obvious that there is much room for improvement in our present method of treatment. . . . Many of the survivors are left permanently blind or deaf, and others become affected mentally. It is a poor satisfaction to save the life of an infant, if it is to remain a deaf mute'.

A. H. Tubby, M.S., F.R.C.S., of the Westminster Hospital, reviews 'Orthopædic Surgery'. Frank A. Rose, F.R.C.S., Assistant Surgeon, Throat Department, St. Bartholomew's Hospital, ends his article on 'Membranous Rhinitis': 'I see no escape from the conclusion that membranous rhinitis is a mild form of diphtheria, and should be treated as such'.

'Notes from Foreign Journals' mention 'a new depilatory paste': sodium mono-sulphide 1 part, quick-lime 1 part, starch-powder 2 parts, sufficient water to make a paste, obtained by Bilouet of the French Army and described as 'an efficient substitute for the use of the razor in the removal of hairs from any part of the body, before operation'.

W. R. B.

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